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The Impact of Naloxone Access Laws on Opioid Overdose Deaths in the U.S.*

Elham Erfanian,[1] Alan R. Collins,[2] and Daniel Grossman[3]

[1] *Resource Economics and Management, Regional Research Institute, West Virginia University, USA*

[2] *Resource Economics and Management, West Virginia University, USA*

[3] *Department of Economics, West Virginia University, USA*

Abstract: Opioid overdoses are the leading cause of unintentional death in the U.S. This research investigates the effects of state-level Naloxone access laws on opioid overdose death rates. Spatial difference-in-differences models reveal that no matter how the access law is measured (either as a binary variable, number of days after the law, or differentiated between access law provisions), the only consistent result is positive indirect effects on overdose death rates. These results indicate that Naloxone access provisions have regional impacts via spillover effects in neighboring states. Looking across multiple provisions, our findings show that, except for third party authorization, there are significant positive effects on overdose death rates. When access laws are evaluated in isolation of any other state level policy response to opioids, increasing access to Naloxone does not reduce overdose death rates, but leads to an overall increase. Thus, the moral hazard problem stemming from this public health policy may be an accurate assessment of the outcome.

Keywords: Opioid overdose death, Naloxone access law, spatial spillovers

JEL Codes: I180, I120, C3

1. INTRODUCTION

Opioid overdose is the leading cause of unintentional death in the U.S. (Visconti et al., 2015). From 2000 to 2014, half a million people in the U.S. died from opioid overdoses, with over 28,000 dying in 2014 alone.[1] Overdose deaths have become such a problem in the U.S. that life expectancy has dropped two years in a row (Stobbe, 2017). When addressing the opioid

*Elham Erfanian is a Ph.D. candidate of Natural Resource Economics at West Virginia University at Morgantown, WV 26506. Alan R. Collins is a Professor of Resource Economics and Management at West Virginia University at Morgantown, WV 26506. Daniel Grossman is an Assistant Professor at West Virginia University at Morgantown, WV 26506. *Corresponding Author:* Elham Erfanian E-mail: elhamerfanian@mix.wvu.edu

[1] For more information, please refer to Rudd et al. (2016)

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crisis as a public health problem, state-level responses can be categorized as either attempts to: (1) limit the supply of opioids through prescription drug monitoring programs or (2) reduce the number of overdoses by authorizing the more widespread provision of overdose reversal drugs, such as Naloxone (Davis and Chang, 2013; Davis et al., 2013, 2014; Beheshti et al., 2015; Davis et al., 2017; Davis and Carr, 2017). Naloxone is a prescription drug that counteracts the effects of an overdose, making it an extremely powerful, though complicated, drug in that its provision may create a false sense of security among drug users.

In this research, we estimate the effect that state level Naloxone access laws have on overdose deaths using a spatial difference-in-differences framework. Given the vast array of literature focusing on opioid overdose death (Visconti et al., 2015; Stobbe, 2017; Scott et al., 2007; Rossen et al., 2013), there is a huge gap in coverage of possible spatial dependency in state and/or county level data. One can easily hypothesize that Naloxone access laws have spatial spillover effects on opioid overdose death rates across states due to factors such as cross-border movement of Naloxone, prescription and illegal drugs, and physician shopping (see Buchmueller and Carey (2018)). Thus, not accounting for spatial dependency in state level data allows for misspecification of the actual impact of these laws on the outcome variable.

To avoid this misspecification bias, the use of a spatial difference-in-differences analysis provides us with estimates of both within state effects and spillover effects among contiguous states from enactment of a Naloxone access law. The extent to which the law expands access to Naloxone varies state by state. The spillover analysis allows us to document biases present in the standard, non-spatial model. We find that Naloxone access laws, either as a binary variable, the days after the law, or when broken down into various provisions,[2] have positive and significant impacts on opioid overdose death rates, and these impacts occur mainly in neighboring states. The impacts of a Naloxone access law within the state itself are not significant except for provisions which provide immunity for criminal and civil liability for a lay person. Thus, important state level spillover effects exist for Naloxone access laws on opioid overdose death rates.

Our main contribution to the literature is development of a Spatial Difference-in-Differences (SDID) framework to investigate the spillover effects of state-level Naloxone access laws on overdose death rates in surrounding states. In addition, we examine the different impacts of specific provisions of access law as explained in Section 2. Enactment of Naloxone access laws demonstrates suggestive evidence of spatial dependence in that neighboring states begin to adopt these laws, especially after 2013.[3] To the best of our knowledge, no previous study has controlled for the spatial interaction between Naloxone access laws and opioid overdose death rates, so the regional aspects of these laws has not been investigated.

The rest of the manuscript proceeds as follows. Section 2 provides background information on trends in opioid overdose and Naloxone access laws. Section 3 provides an empirical model and Section 4 describes the data. In Section 5, we explain the methods and spatial econometric framework utilized, while Section 6 reports the results. We conclude in Section 7 with a discussion and policy implications.

[2]Provisions are identified is Section 2.2.
[3]Available at: http://lawatlas.org/.

2. BACKGROUND

2.1. Opioid Trends

Mortality from opioid overdose has more than quadrupled since 1999.[4] Figure 1 compares opioid overdose death rates among states in 1999 and 2016. Opioid overdose death rates increased during this time period in every state. In 2016, West Virginia had the highest rate of overdose death, while Nebraska had the lowest rate. Between 1999 and 2016, increases in opioid overdose death rates per 100,000 ranged from 0.69 in Arkansas to 38.17 in West Virginia.

Overdoses occur when a person takes a lethal or toxic amount of opiates, such as an illicit drug (e.g. heroin) or prescription medications (e.g. oxycodone).[5] Opiate overdoses can lead to depressed or slowed breathing, confusion, and the lack of oxygen to the brain. Overdoses may occur with legitimate uses of opiates, such as pain relief from a work-related injury.[6]

In 2015, 2.8 million private industry workers and 752,000 public sector workers suffered from nonfatal workplace injuries, many of which led to receiving opioid drug prescriptions, thereby leading to potential abuse, addiction, and/or overdose (Salsberg, 2015). Former Food and Drug Administration head, David Kessler, called the opioid epidemic one of the great mistakes of modern medicine.[7] Workplace injuries served as a driver for prescribing opioids that have the potential to transform into addiction and ultimately overdose and even death.

Reducing opioid abuse and controlling overdose deaths is an important policy goal for both state and federal governments. With a deadlier supply of drugs, controlling the opioid crisis became harder and harder over time.[8] For many years, opioid overdose prevention programs have provided protection services. Since 1996, an increasing number of community-based programs have provided Naloxone (an opioid antagonist) to laypersons in order to reverse the effects of opioid overdose. Narcan TM (Naloxone) is a prescription medicine, but not a controlled substance, that can block the effects of opioids with no life threatening effects on the opiate users.[9,10] Naloxone acts on a persons brain by attaching to the same part of the brain that receives the opioid (OSF, 2017). Once administered, Naloxone takes two to three minutes for its effect to be felt. If an overdose victim does not wake up, a second dose should be administered.

News report examples of Naloxone being used to save lives abound. For instance, Chad Ward, an Emergency Medical Services Supervisor in Huntington, WV, noted that in 2015 there were 944 drug overdoses in Cabell County; but having access to Naloxone allowed him

[4]Available at: https://www.cdc.gov/drugoverdose/epidemic/index.html.

[5]Importantly, many legally prescribed opioids are taken illegally by individuals who were not the original patient.

[6]Available at: https://www.cdc.gov/niosh/topics/prescription/default.html.

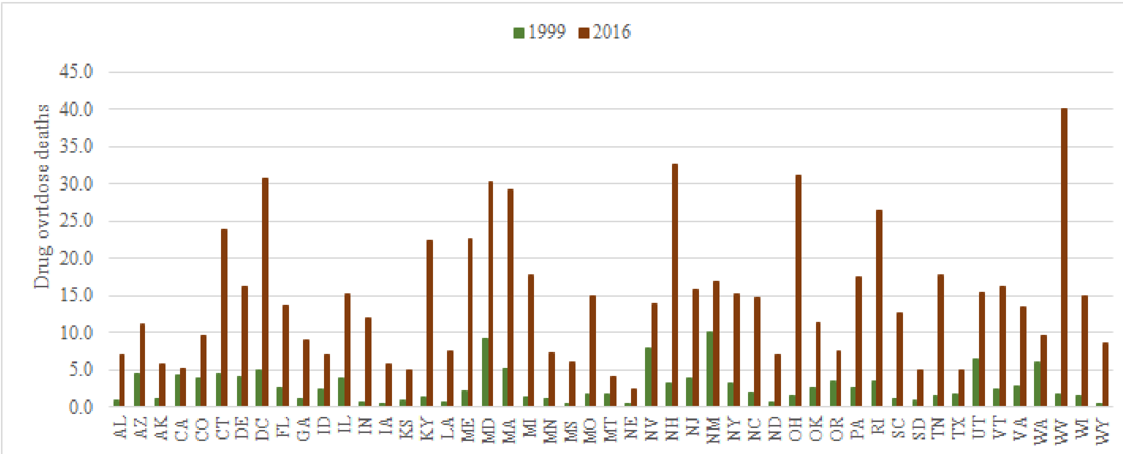
[7]Available at: https://www.cbsnews.com/news/former-fda-head-doctor-david-kessler-opioid-epidemic-one-of-great-mistakes-of-modern-medicine/.

[8]For more information, please refer to: https://www.washingtonpost.com/graphics/2017/health/opioids-scale/?utm$_term = .8748581d9268$.

[9]A controlled substance is generally an opioid or chemical whose manufacture, possession, or use is regulated by a government, such as illicitly used opioids or prescription medications.

[10]Available at: http://stopoverdoseil.org/narcan.html.

Figure 1: Opioid Overdose Death per 100,000 Population by State, 1999 and 2016



Source: CDC-WONDER

to save many patients at the scene of the overdose.[11] In another, more famous example, the musician Prince suffered an oxycodone overdose on April 15, 2016. After being given two doses of Narcan, he recovered. However, six days later, he overdosed for the last time on Fentanyl, a synthetic opioid 50 times more powerful than heroin.[12]

The examples above demonstrate the conflicting viewpoints on Naloxone. Whether Naloxone saves lives or simply delays an eventual overdose death is the paradox at the center of whether it is a solution to the overdose epidemic.[13,14,15,16]

With the recent growth in overdose deaths, interest in assessing the effects of Naloxone access laws and overdose prevention programs on overdose deaths has increased (Walley et al. (2013),Visconti et al. (2015)). Adoption of Naloxone access laws has been found to be associated with a 9 to 11 percent reduction in opioid-related deaths (Rees et al., 2017). McClellan et al. (2018) categorize these laws into Naloxone access and good samaritan laws, and find reductions in opioid-related deaths of 14 and 15 percent, respectively. In a recent working paper, Doleac and Mukherjee (2018) argued that the positive association between Naloxone access laws and opioid-related emergency room visits, along with opioid-related theft, demonstrate a classic moral hazard problem among opioid abusers. For example, providing access to Naloxone may have increased the likelihood individuals took more potent drugs (Doleac and Mukherjee, 2018). One reason for an increase in hospitalizations without a change in deaths for drug overdoses is that Naloxone allows individuals who otherwise

[11] Available at: http://www.wsaz.com/content/news/WSAZ-Investigates-A-Dose-of-Reality-368538771.html.
[12] Available at: https://www.cbsnews.com/news/official-pills-found-at-princes-estate-contained-fentanyl/.
[13] Available at: https://www.nytimes.com/2017/05/09/us/opioids-narcan-drug-overdose-heroin-fentanyl.html?emc=eta1.
[14] Available at: http://www.wsaz.com/content/news/WSAZ-Investigates-A-Dose-of-Reality-368538771.html.
[15] Available at: https://www.cbsnews.com/news/official-pills-found-at-princes-estate-contained-fentanyl/.
[16] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4675355/pdf/nihms742274.pdf

would have died to make it to the hospital. There is a body of literature that shows behavioral responses to different policies (Chan et al., 2015; Lakdawalla et al., 2006; Cohen and Einav, 2003). In another study, Siegler (2015) found a 16 percent decrease in overdose deaths in New York City after the implementation of an overdose prevention program, but his results were not statistically significant for heroin-related overdose mortalities. Similarly, Rees et al. (2017) found statistically insignificant effects of Naloxone access laws on heroin-related deaths in the U.S.

None of these previous research efforts have accounted for the spatial spillovers of access laws between states. Without accounting for spatial spillovers, the results may be biased due to model misspecification. In other words, by ignoring spatial aspects, only within state effects of access laws are examined under the assumptions that both the access law and overdose death rate in one state are totally independent of access laws and death rates in neighboring states. The direction of this bias is ambiguous.

2.2. Naloxone Access Laws

Naloxone has been available by prescription since 1996, although the legal environment for prescribing and dispensing Naloxone varies by state. State legislators have enacted a variety of provisions to expand and to ease prescribing and distributing Naloxone to prevent overdoses. For example, a number of states have enacted laws that involve less civil and criminal liability, whether for prescribers, dispensers, or users (Lim et al., 2016). Davis and Carr (2015) argue that "at-risk" individuals do not have regular contact with professional care givers, so laws and regulations need to ease access to Naloxone beyond traditional prescriptions.

In a traditional Naloxone prescription setting, prescribers prescribe Naloxone to high-risk individuals, such as those who take high doses of opioids. In addition, under this setting, only pharmacists or physicians can distribute Naloxone. Because of the spike in opioid-related deaths, lawmakers and researchers have pushed to make Naloxone available for those most likely to respond to an overdose. The first responders include family, friends, harm reduction program staff, law enforcement officers, emergency medical technicians, and others (Davis and Carr, 2015).

State laws vary in the extent to which they expand the access to Naloxone and/or remove the legal liabilities associated with prescribing, dispensing, or distributing Naloxone (Davis and Carr, 2015). In some states, prescriptions of Naloxone can be provided to third parties or individuals likely to witness an overdose while not being personally at risk of overdose. In some states, prescribers, dispensers, and users are immune from criminal and/or civil liability when administering Naloxone. Additional versions of access laws remove criminal liability for possession of Naloxone. Certain states allow prescribing by a standing order, where prescribers give the authority to pharmacists and other healthcare providers to dispense Naloxone to the person in need (Green et al., 2015; Davis and Carr, 2017). Within states without an access law, Naloxone requires a written prescription by a physician. In these states, physicians who prescribe and individuals who use Naloxone are not immune from criminal and civil liability and professional sanctions.

The list below provided by the Prescription Drug Abuse Policy System (PDAPS) offers a breakdown of Naloxone access law (NAL) provisions into eleven types.[17]

Provision 1: Having immunity from criminal prosecution for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.

Provision 2: Having immunity from civil liability for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.

Provision 3: Having immunity from professional sanctions for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.

Provision 4: Having immunity from criminal prosecution for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.

Provision 5: Having immunity from civil liability for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.

Provision 6: Having immunity from professional sanctions for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.

Provision 7: Prescribers are allowed to provide Naloxone to third parties.

Provision 8: Pharmacists are allowed to dispense or distribute without a patient-specific prescription from another medical professional.

Provision 9: Immunity from criminal liability when administering Naloxone for a Layperson.

Provision 10: Immunity from civil liability when administering Naloxone for a layperson.

Provision 11: Removing criminal liability for possession of Naloxone.[18]

New Mexico was the first state to amend its laws (in 2001) to make it easier for medical professionals to prescribe Naloxone, and for lay administrators to use it without fear of legal repercussions. Table 1 shows the effective date of enacted Naloxone laws starting from 2001. At the end of 2016 a total of 48 states had adopted Naloxone access laws. Thirty-nine of these states allowed standing orders (also called non-patient-specific prescriptions).

As it is shown in Table 2, states tend to implement Naloxone laws by grouping provisions together. For instance, immunity from civil liability for prescribers and dispensers is almost always implemented in the same state during the same year. The exceptions are North Carolina and Ohio. With the exception of Ohio, immunity from criminal liability for prescribers and dispensers is implemented in all the states simultaneously. Immunity from civil and criminal liability for the laypersons follows the same trend. These trends mean that when states implement a specific provision for a category of professional healthcare providers, they

[17] For more information, please refer to: http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139.

[18] Removing criminal liability for possession of Naloxone should increase access and encourage its use in emergency situations (Davis et al., 2013b).

Table 1: Effective Dates of Naloxone Access Laws, 1999-2016

State	Effective Dates of Naloxone Access Laws, 1999-2016
Alabama	June 10, 2015
Alaska	March 15, 2016
Arizona	August 6, 2016
Arkansas	July 15, 2015
California	January 1, 2008
Colorado	May 10, 2013
Connecticut	October 1, 2003
Washington, D.C.	March 19, 2013
Delaware	August 4, 2014
Florida	June 10, 2015
Georgia	April 24, 2014
Hawaii	June 6, 2016
Idaho	July 1, 2015
Illinois	January 1, 2010
Indiana	April 17, 2015
Iowa	May 27, 2016
Kentucky	June 25, 2013
Louisiana	August 15, 2015
Maine	April 29, 2014
Maryland	October 1, 2013
Massachusetts	August 2, 2012
Michigan	October 14, 2014
Minnesota	May 10, 2014
Mississippi	July 1, 2015
Missouri	August 28, 2015
Nebraska	May 28, 2015
Nevada	October 1, 2015
New Hampshire	June 2, 2015
New Jersey	July 1, 2013
New Mexico	April 3, 2001
New York	April 1, 2006
North Carolina	April 9, 2013
North Dakota	August 1, 2015
Ohio	March 11, 2014
Oklahoma	November 1, 2013
Oregon	June 6, 2013
Pennsylvania	November 29, 2014
Rhode Island	June 18, 2012
South Carolina	June 3, 2015
South Dakota	July 1, 2016
Tennessee	July 1, 2014
Texas	September 1, 2015
Utah	May 13, 2014
Vermont	July 1, 2013
Virginia	July 1, 2013
Washington	June 10, 2010
West Virginia	May 27, 2015
Wisconsin	April 9, 2014

Source: Prescription Drug Abuse Policy System (PDAPS)

Table 2: Effective Dates of Naloxone Access Law Provisions, 1999-2016

Year	PR 1	PR 2	PR 3	PR 4	PR 5	PR 6	PR 7	PR 8	PR 9	PR 10	PR 11
2001	NM	NM		NM	NM		NM		NM	NM	
2002											
2003	CT	CT		CT	CT						
2004											
2005											
2006											
2007							NY				
2008	CA	CA		CA	CA						
2009											
2010			IL WA			IL WA	IL WA	IL	IL WA		
2011									CA		
2012	MA						MA		RI	RI	MA
2013	CO NJ NC VT	CO NJ NC VT	CO KY MD NJ	CO NJ VT	CO NJ VT	CO KY MD NJ	KY MD NJ NC OK OR VT VA	KY NJ NC OR VT	CO DC KY NJ NC VT	CO DC KY NJ NC OR VT VA	DC VT
2014	DE GA MN OH PA UT WI	DE GA MI MN OH PA TN UT WI	CA DE GA OH PA RI TN UT WI	DE GA PA UT WI	DE GA MI MN PA TN UT WI	CA DE GA PA RI TN UT WI	CA GA ME MI OH PA RI TN UT WI	CA DE GA MA MN NM NY OK PA RI TN WI	CT GA MA MI MN NY OH PA WI	CT GA MI MN NY PA TN UT WI	MI RI WI
2015	AL AK FL ID IL LA MS NE NV NH ND SC TX WV	AL AK FL ID IN LA MD MS MO NE NH ND SC TX VA WV	AK FL ID LA MS NE NV NH ND SC TX	AL AK FL IL LA MS NE NH NC ND SC TX WA WV	AL AK FL IL IN LA MD MS NE NH NC ND OH SC TX VA WA WV	AK CT FL LA MS NE NV NH ND OH SC TX	AL AK CO CT FL ID LA MS NE NV NH ND SC TX VA WV	AL AK CO CT ID IN LA ME MD MS NV NH ND OH SC TX VA WA WV	AL AK ID LA MS NE NV NH ND SC TX	AL AK FL ID IL IN LA MD MS NE NH ND SC TX WA WV	NV ND TX WV
2016	AZ ME MO SD WA	IA ME SD WA	AZ ME MO SD	AZ CT ME MO SD	ME MO SD	AZ ME MO NM SD	AZ IA SD	AZ FL IA MO SD	ME MO UT WV	AZ IA ME MA MO	IA LA MO NM

Source: http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139 usually implement the same provision for other healthcare providers as well. As a result of this pattern, collinearity issues arise in regression models when including all 11 provisions in an empirical model. Because of this potential collinearity, we group these 11 provisions into five categories for our analysis, which we describe in more detail in the next section.

Numerous studies have analyzed the relationships between Naloxone access laws and overdose deaths (Coffin et al., 2003; Seal et al., 2005; Walley et al., 2013; Davis, 2015; Davis and Carr, 2015; Rowe et al., 2016; Coffin and Sullivan, 2013; Enteen et al., 2010; Green et al., 2008, 2015; Inocencio et al., 2013; Lim et al., 2016; Wheeler et al., 2012). These studies generally investigate the effectiveness of Naloxone access on overdose deaths in observational settings. For instance, according to Wheeler et al. (2012) between 1996 and 2014, community organizations provided Naloxone rescue kits to 152,283 laypersons and received reports of 26,463 overdose reversals. Evidence of Naloxone access laws as a public health response to the opioid crisis being an overdose prevention tool on both nationwide and regional scales is still mixed. In this study, we employ state level analyses using the dates of enactment for Naloxone access laws to investigate the spillover effects on opioid overdose death rates.

3. EMPIRICAL MODELS

Empirical studies have shown that a number of factors influence opioid overdose deaths in the U.S. Table 3 shows the important variables, study region, their impact on overdose deaths, and references. However, the opioid epidemic literature is lacking investigations that include the effects of high-risk injury occupations such as mining, manufacturing, and constructions, availability of drug prescriptions, and heroin related crime (as an indicator for availability of heroin) on opioid overdose deaths.

The difference-in-differences (DID) technique is an econometric tool first applied in the 19$^{\text{th}}$ century to control for before-and-after implementation of a treatment or policy[19] (National Research Council, 2004). A standard DID model to evaluate the effects of a Naloxone access law by differentiating between treatment and control (untreated) states is represented by:

$$TODDrate_{it} = \alpha_0 + \alpha_1 X_{it} + \alpha_2 NAL_{it}T_{it} + \nu_i + \omega_t + \epsilon_{it} \tag{1}$$

where $ODDrate_{it}$ is the opioid overdose death rate in state i in year t. X_{it} is a vector of time-varying covariates that control for factors influencing death rates such as those listed in Table 3. $NAL_{it}T_{it}$ is the DID variable which takes a value of 1 if the state had a Naloxone access law in that particular year and zero otherwise.[20] ν_i is an unobservable, time-invariant state effect, which subsumes the main effect of the Naloxone law, while ω_t is a vector of year fixed effects which subsumes the main effect of the variable T (time). ϵ_{it} is an error term.

The standard DID model presented in Equation (1) raises a possible issue with endogeneity for the NAL variable, i.e. does the level of a states opioid overdose death rate influence enactment of a Naloxone access law in that state? We tested for this by examining state overdose death rates in the year prior to enactment of an access law compared to rates in

[19] More information is available at: https://www.mailman.columbia.edu/research/population-health-methods/difference-difference-estimation.

[20] In Rees et al. (2017), those states that had a law in effect for less than a full year had NAL as a fraction.

Table 3: List of the Variables Utilized in Overdose Death Research

Variable	Study Region	Coefficient Sign	Reference
Poverty	New York City districts	+	Marzuk et al., 1997
Income distribution	New York City neighborhoods	-	Galea et al., 2003 Nandi et al., 2006
External characteristics of neighborhood	New York City neighborhoods	-	Hembree et al., 2005
Internal characteristics of neighborhood	New York City neighborhoods	-	Hembree et al., 2005
Police activity	New York City neighborhoods New York City police precinct	+	Nandi et al., 2006 Bohnert et al., 2011
Unemployment	Italy provinces	-	Gatti et al., 2007
Per capita GDP	Italy provinces	+	Gatti et al., 2007
Urbanization	Italy provinces	+	Gatti et al., 2007
Couples separation	Italy provinces	+	Gatti et al., 2007
Demographic factors (African-American men)	Chicago neighborhoods	+	Scott et al., 2007
Location relative to the U.S.-Mexico border	New Mexico counties	-	Shah et al., 2012
Heroin source/type, price and purity	27 U.S. MSAs	+/-	Unick et al., 2014
Educational attainment	U.S states	-	Richardson et al., 2015
State medical cannabis laws	U.S states	-	Bachhuber et al., 2014
Uninsured adults and health care cost	New Mexico counties	-	Shah et al., 2012
Substance Abuse Insurance Mandates	U.S states	-	Selby, 2017

states without an access law. To account for different years of means, we subtracted the state means from the national mean in that year (for non-access law states, 2014 overdose death rates are used). A t-test showed no statistical difference between access law and no access law states (t = -0.611, p =0.544). Based upon this evidence, Endogeneity in equation (1) is not seen as an issue.

Under a non-spatial econometric estimation, observations do not depend on location (LeSage and Pace, 2009; Elhorst, 2014). Each observation is an independent point and therefore there is no correlation between each point and its neighbors. In non-spatial models, each observation has a mean of $x_i\beta$ and a random component ϵ_i where the observation i represents a region or point in space at one location and is considered to be independent of observations in other locations. In other words, independent or statistically independent observations imply that $E(\epsilon_i\epsilon_j) = E(\epsilon_i)E(\epsilon_j) = 0$. This assumption of independence greatly simplifies models.

In many cases, this assumption is not applicable and observations located at different points or regions are dependent on one another (LeSage and Pace, 2009). Suppose we have two regions (neighbors) i and j. If these two regions are spatially correlated and normality of error terms is assumed, then:

$$y_i \longleftrightarrow y_j \tag{2}$$

where the dependent variable (y) in region j influences the dependent variable in its neighbor region i and vice versa.

All spatial models have a weight matrix (W), which quantifies the spillover between regions. Elhorst (2014) expresses the weight matrix as a tool to describe the spatial arrangement of the geographical units in the sample. There are a variety of units of measurement for spatial dependency such as neighbors, distance, and links (Getis, 2007).[21] In this study, we conducted and applied different weight matrices and chose the appropriate contiguity weight matrix based on the nature of the research. As Debarsy et al. (2012) point out, given the cross-border shopping of goods a weight matrix for neighbors with border touching seems intuitively appealing.

The use of spatial difference-in-differences (SDID) models has gained attraction in urban economics in recent years (Hembree et al., 2005; Dubé et al., 2014; Sunak and Madlener, 2014). However, to the best of our knowledge, few studies perform SDID model in public health and public policy research (de Andrade, 2016; Chagas et al., 2016) are noted exceptions). We argue that opioid overdose death rates and Naloxone access laws need to be evaluated within a regional framework. For example, adoption of an access law in one state could be followed by surrounding states. Marijuana legalization status in U.S. states is a good example of mimicking law enactment in neighboring states. In such cases, not only would opioid overdose death rates be affected by its own state level variables, but it also may be affected by neighboring state control variables.

Since medications like Naloxone can be rather easily transferred across state borders, users can buy Naloxone in a neighboring state with an access law and use it in their home state without an access law. This type of transmission of Naloxone across state borders could affect the opioid overdose death rates in neighboring states. In addition, the opioid epidemic in the U.S. is observed to be clustered in specific regions such as Appalachia and the Southwest[22,23] (see Rudd et al. (2016)). Therefore, analyzing the effectiveness of the Naloxone access law on opioid overdose deaths is more appropriate to investigate within a regional framework rather than a standard state level analysis.

When a spatial component (whether it is the spatial component of the dependent variable, control variables, or the error term) is statistically significant, the coefficients estimated by non-spatial models would be biased or inefficient. For example, if the spatial component is just in the error term, estimated coefficients in the non-spatial model are still unbiased and consistent, but not efficient (Case, 1991). In addition, variances may be non-efficient in non-spatial models (Griffith, 2005; LeSage and Pace, 2009). Accordingly, statistical tests such as t- and F-tests may be invalid, leading researchers to interpret their results improperly.

We conduct the estimation process by adding a spatial component to the non-spatial econometric analysis in a panel data framework. The SDID model developed for opioid overdose death rate can be written as

[21] For more details on the differences between the spatial weight matrices, please refer to Elhorst (2014) and Getis (2007).

[22] For more details, please refer to: http://www.realclearhealth.com/articles/2017/06/14/analysis_peering_into_the_nations_opioid_crisis_through_a_regional_lens_110633.html.

[23] For more details, please refer to: http://www.acutisdiagnostics.com/sites/default/files/Peeling_Back_the_Curtain_on_Regional_Variation_in_the_Opioid_Crisis_FINAL_June_2017%20%281%29.pdf.

$$\begin{aligned} TODDrate_{it} =& \beta_0 + \beta_1 NAL_{it} T_{it} + \sum \beta_j X_{ijt} + \rho WTODDrate_{jt} + \vartheta WNAL_{jt} T_{jt} \\ &+ \theta WX_{jt} + \nu_i + \omega_t + \epsilon_{it} \end{aligned} \tag{3}$$

where *TODDrate* stands for the opioid overdose deaths per 100,000 populations in state i and time t, *NAL* represents a dummy variable for whether or not the state has a Naloxone access law in a given year. X is a vector of demographic variables described above, while ν_i and $\omega_t$are state and year fixed effects, respectively. The terms *WTODDrate*, *WNALT*, *WX* denote the spatial components of opioid overdose death rate, Naloxone access law, and other control variables, respectively. ρ, ϑ, and θ represent the spillover effects of the dependent variable and independent variables, respectively. These variables explain the effects of dependent variable and independent variables of neighboring states, j, on the dependent variable in specific state, i.

We examine the impact of Naloxone access laws with three different models. First, following Rees et al. (2017), we impose a dummy variable for passage of a Naloxone access law at the state level in Model 1. For Model 2, we assess the impact of access laws by the number of days since the effective date of the law.[24] To examine the impacts of access laws over time, a quadratic form of this variable was included in this model. Finally, Model 3 provides for a breakdown of access laws by their specific provisions. Since Naloxone access laws are not homogenous, to evaluate the effects of access laws on opioid overdose death rates, one needs to differentiate between the provisions included in each law. Keeping NAL 1 for the binary variable in Model 1, we control for access law provisions by imposing five binary variables in Model 3 with grouping provisions to avoid collinearity:

NAL 1: Having a Naloxone access law.

NAL 2: Immunity from criminal liability, civil liability, and professional sanctions for prescribing, dispensing or distributing Naloxone to a layperson for prescribers and dispensers.

NAL 3: Third parties' authorization to prescribe Naloxone.

NAL 4: Pharmacists are allowed to dispense or distribute Naloxone without a patient-specific prescription from another medical professional.

NAL 5: Immunity from criminal and civil liability administering Naloxone to a layperson.

NAL 6: Removing criminal liability for possession of Naloxone.

A priori, we expect these Naloxone access laws to be associated unequivocally with greater access to Naloxone. However, whether these laws lead to improvements in drug overdose rates remains an open question. Due to the overdose-reversing properties of Naloxone, we expect improved access to reduce overdose deaths. However, if as others have found, Naloxone leads to individuals behaving in riskier ways by taking more potent drugs or larger amounts of drugs, we may expect access to increase drug deaths. While understanding how each different provision will affect individuals is a goal of this research, ultimately, the sign and magnitudes of these effects are empirical questions.

For the X vector of control variables, there is some evidence in the literature that poverty, unemployment, uninsured rate, and income inequality are each positively correlated with opioid overdose deaths (Galea et al., 2003; Nandi et al., 2006; Gatti et al., 2007; Shah et al., 2012). Conversely, income and education have negative relationships with opioid overdose deaths (Richardson et al., 2015). We expect to see positive effects from the availability

[24]The days after law is measured by counting the days from the effective date to the last day of the year.

of legal and illegal opioids on opioid overdose death rates. Medical marijuana laws are expected to have a negative effect on opioid overdose death rates because we expect opioids and marijuana to be substitutes so that medical marijuana laws will likely reduce the cost of receiving marijuana and therefore decrease the quantity of opioids demanded.

4. DATA

Data for constructing the three models come from a variety of sources. We use data from the Centers for Disease Control and Prevention (CDC) Wonder for 1999-2016[25] which contain the universe of opioid overdose deaths and opioid overdose death rates by state in the U.S. We focus on the 48 continuous states of the U.S. and Washington, D.C. over this time period, due to Alaska and Hawaii not having obvious neighbors to measure spatial spillovers. These data were compiled using underlying cause of death compressed mortality files. The number of opioid overdose deaths by state were classified using the International Classification of Diseases, Tenth Revision (ICD-10). We included overdose deaths coded as unintentional (X40-X44), homicide (X85), undetermined intent (Y10-Y14), and suicide cases (X60-X64).[26] Among deaths with opioid overdose as the underlying cause, the type of opioid involved is indicated by the following ICD-10 multiple cause-of-death codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); heroin (T40.1); natural and semisynthetic opioids (T40.2); methadone (T40.3); and synthetic opioids other than methadone (T40.4). The dependent variable unit is the number of opioid overdose deaths per 100,000 populations. Population data are collected from the Centers for Disease Control and Prevention (CDC) Wonder.

For our variable of interest, we create measures of whether each state had a Naloxone law, the various provisions of each law, and effective dates from the Prescription Drug Abuse Policy System (PDAPS[27]). For control variables in the X vector, Unick et al. (2014) recommend including illicit drug price. Since we do not have access to such data for our time frame, we instead control for drug arrests and quantity of prescription drug sales. Sale and possession related arrests of opium or cocaine and their derivatives (Morphine, Heroin, and Codeine) were provided by the Federal Bureau of Investigation to control for illicit opioids supply. The availability of prescription opioids comes from controlled substances transactions of prescriptions available through Automated Reports and Consolidated Ordering System (ARCOS).[28]

State level economic variables of per pupil spending on education, the poverty rate, the unemployment rate, population density, and the uninsured rate were obtained from the U.S. Census Bureau. Income inequality, high school attainment, and the college attainment data were obtained from U.S. state-level income inequality data and annual state-level measures of human capital attainment at Mark W. Frank home page.[29] Per capita personal income was based on the information provided by Federal Reserve Bank of St. Louis (FRED).[30] Employment in mining, construction, and manufacturing and the size of the total labor force

[25] National Vital Statistics System (NVSS).
[26] As a robustness check we test the total number of opioid overdose deaths as the dependent variable (not restricted to ICD-10 codes recommended by Ruhm (2016)).
[27] Available at: http://pdaps.org/.
[28] Available at: https://www.deadiversion.usdoj.gov/arcos/retail_opioid_summary.
[29] Available at: http://www.shsu.edu/eco$_m wf/inequality.html$.
[30] Available at: https://fred.stlouisfed.org/release?rid=151.

Table 4: Descriptive Statistics

Variable	Mean	Standard Deviation	Min	Max	Expected coeff. sign
Opioid overdose death rates (per 100K pop)	7.05	5.12	0.26	40	
Total opioid overdose death rates (per 100K pop)	7.38	5.32	0.19	41.80	
NAL 1	0.173	0.363	0	1	-
NAL 2	0.136	0.328	0	1	-
NAL 3	0.135	0.327	0	1	-
NAL 4	0.096	0.276	0	1	-
NAL 5	0.133	0.323	0	1	-
NAL 6	0.032	0.168	0	1	-
Days after Naloxone access law (days/1000)	0.234	0.712	0	5.745	-
Square of the days after Naloxone access law ($days^2$/1000)	349	1,978	0	25,150	+
Presence of Medical marijuana law	0.25	0.43	0	1	-
Heroin arrest rate (arrests/100k pop)	138.05	103.15	0.61	761.43	+
Opioid prescription (kg/100k pop)	56.527	41.023	6.911	496.506	+
Employment ratio (%)	0.14	0.04	0.002	0.26	+
Population density (pop./mi2)	342.31	1,242.48	5.028	10,013	-/+
Income inequality (income share for the top %10) (%)	44.72	4.98	33.27	62.17	
College attainment (the total number of college graduates/ the total state population) (%)	0.19	0.04	0.10	0.46	-
Spending on education ($1000)	9.22	2.83	4.16	20.60	-
Poverty rate (%)	13.38	3.34	5.60	23.90	+
Unemployment rate (%)	5.71	2.06	2.30	13.70	+
Uninsured rate (%)	12.69	4.14	3.00	26.10	+
Median HH income (thousand dollars)	47.15	8.36	29.29	76.16	-
Per capita income (thousand dollars)	38.03	9.09	20.56	70.75	-
Number of observations			882		

were collected from Bureau of Labor Statistics (BLS).[31] To compute the employment ratio for high-risk injury occupations, we added the number of individuals employed in mining, manufacturing, and construction, and divided it by the total labor force. Medical marijuana law data were collected from the leading source for pros and cons of controversial issues.[32] Finally, the spatial weight matrix (a shape file of U.S. states consisting of the latitudinal and longitudinal coordinates of all the 48 states and D.C.) was adapted from the U.S. Census Bureau (Tiger) report.

To control for spillover effects of Naloxone access laws, the 48 continuous U.S. states plus District of Colombia were included in our analysis. In spatial analysis, contiguity and neighborhoods play vital roles (Tobler, 1970). We focused on contiguous states based on the first law of geography: everything is related to everything else, closer things even more so (Tobler, 1970). Descriptive statistics for each variable are reported in Table 4 along with the expected signs of Naloxone access law and control variables. Following previous studies (Rees et al., 2017) which found a negative effect of Naloxone access laws on opioid overdose deaths, we expect to have a negative effects of the law on opioid overdose death rates.

[31] Available at: https://www.bls.gov/sae/data.htm.
[32] Available at: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.

Table 5: Moran's I Index for State Level Opioid Overdose Death Rates

	1999	2016
Moran's I	0.407	0.581
z-statistics	5.413	5.842
p-value	0.01	0.000

5. METHODS

5.1. Exploring Spatial Dependency in Opioid Overdose Death Rates across States

As we mentioned in the previous section, the economic distance concept is the motivation for spatial spillover effects. Before analyzing spatial dependency by corresponding econometric models, an intuitive way to identify clusters is by looking at a map of overdose death rates. As shown in Figure 2, opioid overdose death rates have increased over time. In 1999, only two states had an overdose death rate between 8 and 10 deaths per 100,000 population. By 2016, 34 states had overdose death rates between 8 and 40 deaths per 100,000 population. Also, some spatial clusters are obvious especially in 2016. New Mexico had the highest opioid overdose death rate in 1999. In 2016, its surrounding states also had high rates of overdose deaths. Substantial clustering also exists within states on the east coast.

Given the fact that opioid overdose death rates show visual evidence of clustering among states, the next step is to detect spatial autocorrelation. Spatial autocorrelation measures the interrelationship of opioid overdose death rates across neighboring states. A common index used to discover spatial autocorrelation is the Global Morans I index.[33] As pointed out by Chen and Haynes (2015), Moran's I is a test on a yearly basis. A significant and positive z-value for Moran's I index implies a positive spatial autocorrelation. Table 5 shows the results for Moran's I index for two points of time and its z-statistics and p-value. These tests reveal that there has been and still is (as of 2016) significant spatial autocorrelation among state level opioid overdose death rate in the U.S. This means state level opioid overdose death rates tend to be clustered together.

Moran's I index assesses the overall presence of spatial autocorrelation. This index could offset the effects of spatial autocorrelation if some observations have a positive spatial autocorrelation while the others show a negative spatial autocorrelation. For further examination, we also report the results of Moran's I scatter plot test. Scatter plots shows observations in four different quadrants: High value observation surrounded by high value observations (i.e. QI: HH) and 3 other clusterings for LH (QII), HL (QIV), and LL (QIII) quadrants. Figure 3 provides Moran scatter plots of the U.S. opioid overdose death rates in 1999 and 2016. This figure illustrates that in both years, most of the states with high overdose rate are adjacent to states with high overdose rates. This also is true for the states

[33]More information is available at: http://ceadserv1.nku.edu/longa//geomed/ppa/doc/globals/Globals.htm.

Figure 2: Opioid overdose death rates in the U.S. 1999 and 2016

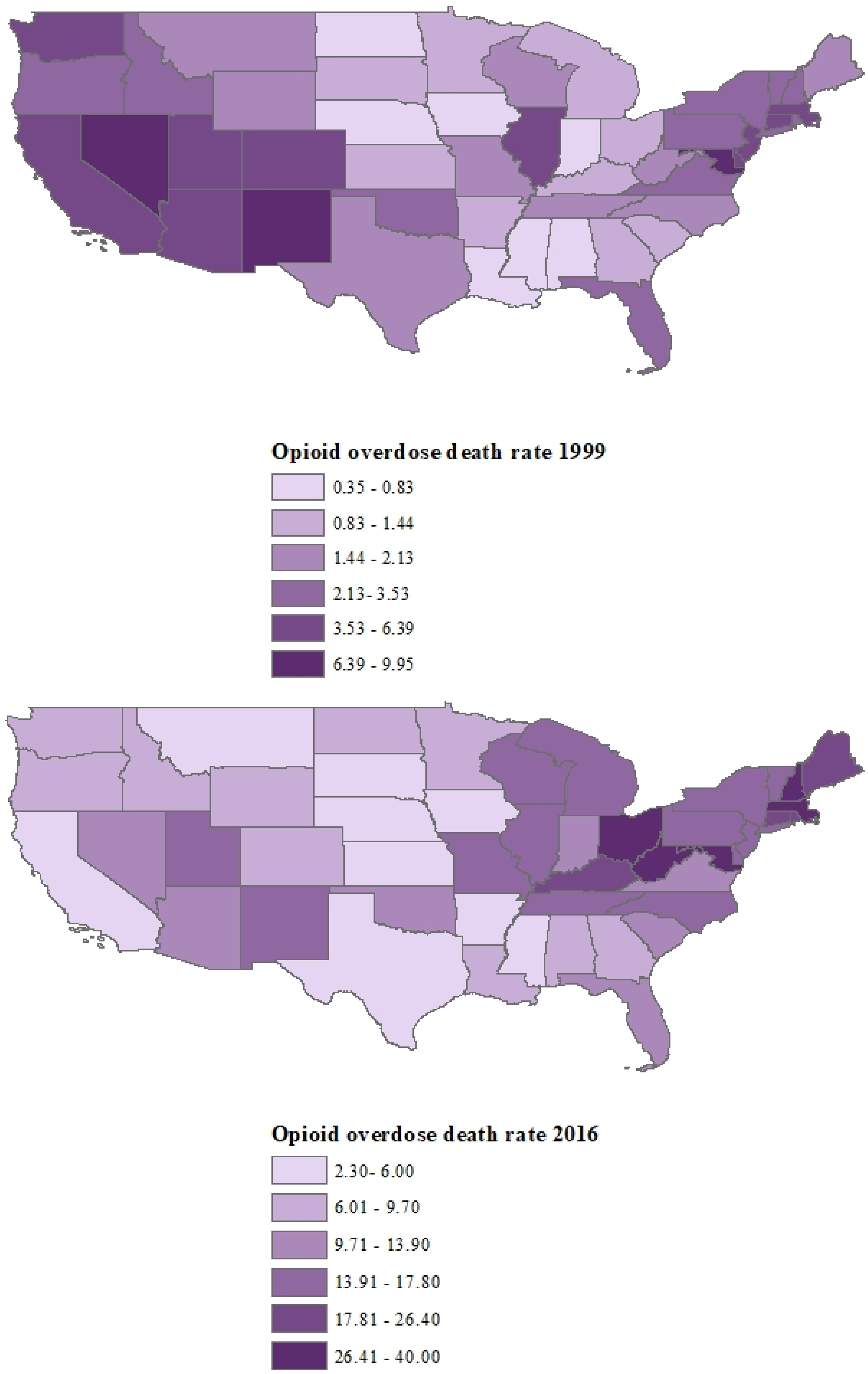
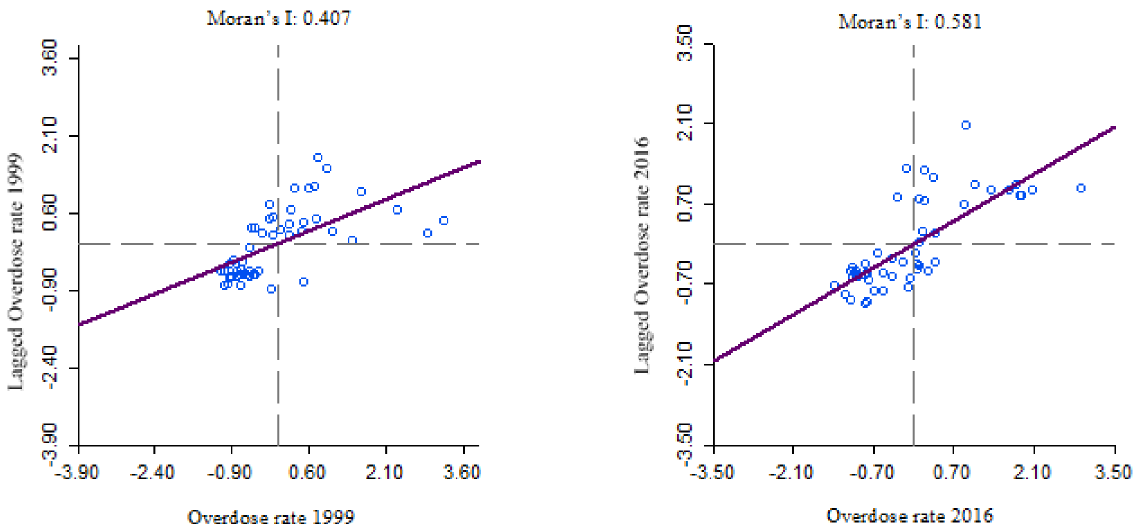


Figure 3: Moran's I Scatter Plot of State Level Opioid Overdose Death Rates (1999 and 2016)



with low overdose death rates. Thus, we apply a first-order contiguity weight matrix in our spatial analysis.

The existence of statistically significant spatial autocorrelation among states implies that the ordinary least square estimations (non-spatial models) may lead to biased estimates. Therefore, it is appropriate to apply spatial models in the analysis of Naloxone access laws and opioid overdose death rate. As Delgado and Florax (2015) point out, identification of causal effects is no longer valid if the Stable Unit Treatment Value Assumption (SUTVA)[34] is violated. A SUTVA violation means that in determining the treatment effect, considering ones own treatment status is not sufficient. Treatment status of neighboring regions (in our case states) has to be taken into account as well (Delgado and Florax (2015)).

5.2. Spatial econometric analysis

There are five different spatial models. The first one is the spatial autoregressive lag model (SAR) where the dependent variable in neighbor j influences the dependent variable in neighbor i and vice versa. Second, a Spatial Error Model (SEM) assumes dependency in the error term. SLX model or spatial lag of control variables assumes that only control variables play a direct role in determining dependent variables. Lastly, there are Spatial Durbin Model (SDM) and Spatial Error Durbin Model (SDEM) that include spatial lags of the control variables as well as the dependent variable and a spatial lag of the control variables (WX), as well as spatially dependent disturbances.

As discussed above and based upon the results of the spatial analysis, we have strong

[34]Stable Unit Treatment Value Assumption: potential outcomes for person i are unrelated to the treatment status of other individuals.

reasons to suspect that spatial spillovers are important both theoretically and empirically when examining the effect of access policy for both state and temporal variation. To evaluate the effects of Naloxone access laws on opioid overdose death rates, we first test a general non-spatial specification against SAR and SEM models by conducting a Lagrange Multiplier (LM) test. In both cases, the spatial models were the appropriate specification[35] (LM for non-spatial against SAR = 45.51 and p-value = 0.00, LM for non-spatial against SEM = 10.01 and p-value = 0.00). The next step is testing SAR against SEM. By applying the robust LM test, we failed to reject that the SAR model is the most appropriate specification (LM spatial lag = 148.37 > LM spatial error = 112.86). Knowing that the SAR, SEM, and SLX models are nested within SDM and SDEM, for applied works LeSage (2014) recommends applying either a SDM or SDEM[36], we continue our estimations by focusing on the SDM model which is a global spatial econometric model encompassing both SAR and SLX models.[37]

In addition to applying Lagrange multiplier, LM spatial lag, and LM spatial error tests, we also applied Bayesian posterior model probabilities to compare SDM and SDEM specifications. Consistent with the results from the LM tests, this analysis provides further support of the SDM specification in our context.

6. SPATIAL RESULTS

Due to the cross border issues of Naloxone and opioid drugs, it is important to consider the spillover effects between states in regards to overdose death rates and Naloxone access laws. We argue that a first-order contiguity weight matrix is the right choice for several reasons. First, we need the weight matrix to be exogenous to our estimation, and a first-order contiguity matrix fits this requirement. Secondly, geographical proximity has been shown to be important for spillovers (e.g., Jaffe (1989), Jaffe et al. (1993), Varga (1998), Chagas et al. (2016)).

Table 6 presents the spatial regressions results for Models 1 and 2 presented in Section 3. Within these two models, there are no statistically significant, direct effects of Naloxone access laws on overdose death rates. The fact that our direct effect results are small and statistically insignificant suggests that Naloxone laws do not affect overdose rates in the state they are enacted. Indirect effects, however, are positive and statistically significant. When direct and indirect effects are combined, both models show positive impacts, meaning that opioid overdose death rates increase following the implementation of Naloxone access laws, with the majority of this effect coming through spatial spillovers.

This may seem like a counterintuitive result, i.e., that a more lax legislative environment for Naloxone in a state leads to more deaths in surrounding states. However, it is important to note that Doleac and Mukherjee (2018) found evidence of higher hospitalization rates in states following Naloxone laws and some evidence of regional increases in deaths. They also

[35] For more information, please refer to Florax et al. (2003).

[36] For more information, please refer to LeSage (2014).

[37] As noted by LeSage (2014), cross-border shopping has a local spillover rather than a global spillover. We argue that in the case of legal prescriptions and illicit drugs, drug transfers occur through more than just neighboring states. In addition, state legislatures may adopt Naloxone access laws based upon neighboring states overdose death rates and the adoption of an access law.

note evidence of increased fentanyl use, a much more potent opiate than even heroin.

Model 3 differentiates between laws by breaking them down into five provision groupings.

Table 6: Impact of Access Laws on Opioid Overdose Deaths

Determinants	Model 1		Model 2	
	Direct	Indirect	Direct	Indirect
Naloxone access law 1	0.238	5.767***	-	-
	(0.554)	(0.000)		
Days after NAL 1 law	-	-	0.251	7.656***
			(0.583)	(0.007)
Days after NAL 1 law^2	-	-	-0.00001	-0.001***
			(0.233)	(0.000)
Medical marijuana law	1.318***	2.687*	1.109**	1.772
	(0.001)	(0.058)	(0.010)	(0.217)
Heroin related arrest	0.008***	0.007	0.008***	0.009*
	(0.000)	(0.225)	(0.000)	(0.086)
Opioid prescription	0.010***	0.021*	0.011***	0.024**
	(0.000)	(0.098)	(0.002)	(0.048)
Employment Ratio	34.104***	-68.280**	36.500***	-59.90*
	(0.002)	(0.039)	(0.001)	(0.061)
Population density	0.002**	-0.006	0.014	0.142
	(0.032)	(0.327)	(0.352)	(0.826)
Income inequality index	-0.011	-0.035	-0.015	-0.052
	(0.825)	(0.817)	(0.757)	(0.736)
College graduate	-0.060	0.118	-0.034	0.151
	(0.434)	(0.633)	(0.653)	(0.536)
Education spending per student	0.116	-0.045	0.124	-0.019
	(0.431)	(0.921)	(0.425)	(0.966)
Poverty	0.169	1.570***	-0.043	1.210
	(0.307)	(0.004)	(0.791)	(0.822)
Unemployment	-0.161	-0.529	-0.163	-0.359
	(0.205)	(0.186)	(0.198)	(0.353)
Uninsured	0.052	0.333*	0.071	0.420**
	(0.321)	(0.052)	(0.195)	(0.025)
Per capita income	-2.130***	4.246*	-2.571***	1.84
	(0.002)	(0.096)	(0.000)	(0.474)
ρ		0.49		0.48
		(0.000)		(0.000)
R^2		0.85		0.85
Observations		882		882

Note: P-values in parenthesis
*, **, and *** refer to 10% 5%, and 1% significance levels, respectively.

Table 7 shows the estimation results for access laws by provision. Given the statistically significant spatial autocorrelation coefficient (ρ), the parameter estimates in the two-way fixed effects spatial autoregressive model cannot be interpreted as non-spatial models. We estimate the direct and indirect effects to yield an interpretation of the spatial spillover effects. These results show similar outcomes to Models 1 and 2 when we break down these laws by their provisions. With the exception of provisions of immunity from criminal and civil liability for administering Naloxone, the direct effects on overdose death rates are small and statistically insignificant, showing no evidence of reducing these rates. This direct effect suggests that some aspect of removing criminal liability of Naloxone distribution makes individuals more likely to fatally overdose. We can only speculate that perhaps this provision removes a stigma from taking drugs and further serves as an implicit approval to take more potent drugs (Doleac and Mukherjee (2018)) or that Naloxone laws are correlated with fentanyl distribution.

Out of five provision groupings, immunity from criminal liability, civil liability, and professional sanctions for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers and dispensers (NAL 2), the ability of prescribers to provide Naloxone to third parties (NAL 3), immunity from criminal and civil liability administering Naloxone to a layperson (NAL 5), and removing criminal liability for possession of Naloxone (NAL 6) have statistically significant indirect effects. NAL 2, NAL 5, and NAL 6 increase overdose death rates in the neighboring states where they are enacted, while the ability of prescribers to provide Naloxone to third parties decreases overdose death rates in the neighboring states. In each case, indirect effects are much larger than direct effects, from about 5 to 15 times greater than the corresponding direct effects. For total effects, NAL 5 and NAL 6 are statistically significant and positive; while NAL 3 is significantly negative (Table 7). Thus, while both negative and positive impacts on overdose death rates are found for Naloxone access law provisions; positive impacts via spillover effects dominate the outcome of these laws.

While these spillover effects are large, we caution restraint when interpreting these coefficients. Previous research has differed on the effect of Naloxone laws on overdose deaths. Our direct effect results are small and statistically insignificant, suggesting that Naloxone laws do not affect overdose rates in the state they are enacted. Several reasons may explain the size and direction of these spillover effects. First, these laws may be enacted in neighboring states because of perceived drug risk or even drug deaths occurring in nearby states.[38] Additionally, the positive and statistically significant indirect effects of access laws may be explained by their potential impacts on the increased availability of high potency drugs (like heroin) in neighboring states. Our logic is that increased access to Naloxone keeps opioid drug abusers alive longer and leaves them seeking higher potency drugs, thus leading to more of these drugs flowing through illegal drug supply channels across multiple states.

Other influences on opioid overdose death rates include heroin related arrests and opioid prescription with positive and significant direct, indirect (only opioid prescription), and total effects (Table 7). Heroin related crime and prescriptions of opioids both increase opioid overdose death rates. Opioid prescription increases the overdose death rates within the state as well as surrounding states, while heroin related crime increases the overdose death rate only within the state. Employment of those who work at mining, construction, and manufacturing industries also increases opioid overdose death rates within the state while decreasing rates in neighboring states.

Per capita income has a significant and negative direct effect on opioid overdose death rates. The implication is that states with higher per capita incomes have lower opioid overdose death rates, while states with lower per capita incomes suffer from higher opioid overdose death rate. Contrary to our expectations, states which passed a medical marijuana

[38] We thank an anonymous referee for making this point.

Table 7: Direct, Indirect, and Total Effects of SDM Model

	Direct Effect	Indirect Effect	Total Effect
Naloxone access law 2	-0.199	2.970**	2.771
	(0.710)	(0.016)	(0.178)
Naloxone access law 3	-0.555	-5.948***	-6.503**
	(0.382)	(0.006)	(0.013)
Naloxone access law 4	-0.237	4.165	3.928
	(0.708)	(0.102)	(0.179)
Naloxone access law 5	1.994***	9.659***	11.653***
	(0.009)	(0.001)	(0.001)
Naloxone access law 6	0.373	5.710**	6.084**
	(0.539)	(0.012)	(0.017)
Medical marijuana law	0.815*	0.308	1.124
	(0.059)	(0.825)	(0.504)
Heroin related arrest	0.008***	0.005	0.014**
	(0.000)	(0.116)	(0.006)
Opioid prescription	0.012***	0.030**	0.042***
	(0.000)	(0.016)	(0.003)
Employment Ratio	31.699***	-49.547	-17.847
	(0.003)	(0.116)	(0.003)
Population density	0.001**	-0.002*	-0.0003
	(0.214)	(0.744)	(0.957)
Income inequality index	-0.008	-0.026	-0.034
	(0.868)	(0.859)	(0.835)
College graduate rate	-0.048*	0.163	0.114
	(0.508)	(0.491)	(0.678)
Education spending per student	0.155	0.432	0.587
	(0.289)	(0.322)	(0.240)
Poverty rate	0.011	0.636	0.647
	(0.941)	(0.218)	(0.257)
Unemployment rate	0.035	0.274	0.310
	(0.787)	(0.518)	(0.500)
Uninsured rate	-0.0007	0.030	0.030
	(0.987)	(0.855)	(0.877)
Per capita income	-2.179***	3.584	1.404
	(0.002)	(0.149)	(0.614)
ρ		0.47	
		(0.000)	
R^2		0.86	
Observations		882	

Note: P-values in parenthesis
*, **, and *** refer to 10% 5%, and 1% significance levels, respectively.

law have slightly higher overdose death rates. Other variables (income inequality, education spending per student, poverty rate, and uninsured rate) do not have statistically significant effects on overdose death rates.

In terms of control variables, our results are consistent with those found by Keyes et al. (2014), but contradict Gatti et al. (2007). One possible reason for the difference with the Gatti et al. (2007) study is that they focus on Italy, which may be very different from our U.S. based analysis.

Finally, as a robustness check, a new dependent variable of total opioid overdose death rates introduced in Section 4 is examined. As pointed out by Rees et al. (2017), opioid overdose deaths published by CDC is based on the underlying cause of death (accidental, intentional, and undetermined intent), for example Ruhm (2016). For this check, the new dependent variable represents a comprehensive and unrestricted measure of opioid overdoses using Model 3. The relative magnitude and sign for all statistically significant effects from Naloxone access law provision groupings and all other variables are unchanged from Table 7.[39]

7. CONCLUSIONS

Opioid overdose deaths are the leading cause of unintentional death in the U.S. These drugs are associated with more deaths than car accidents and guns. To address this nationwide public health emergency, state governments have implemented Naloxone access laws to ease access to this overdose reversal drug. In this research, we examine the impact of these Naloxone access laws on opioid overdose deaths and their spillover effects to surrounding states. No endogeneity between overdose death rates and access laws is found to exist.

We applied spatial econometrics models to avoid potential bias in coefficient estimation and our regression results from all three models indicate no matter how we control for Naloxone access laws, we find no statistical evidence to show that Naloxone access laws help reduce drug overdose death rates in the adopting state. When measuring Naloxone access laws in three different ways, positive spillover effects of these laws are statistically significant and dominate direct effects in terms of magnitude. Thus, Naloxone access laws have more regional than state level effects. We are the first study to explore the spatial spillovers of these Naloxone access laws across states.

It is useful to compare the magnitude of the aggregate effects from groupings of Naloxone access law provisions with the effects for heroin related arrests and drug prescriptions. To do that, we use state level means to compare relative magnitudes. For example, if an overdose prevention policy could reduce opioid prescriptions by 50 percent, the impact of this policy would reduce opioid overdose death rates by slightly over one per 100,000 population. Conversely, the total effect of enactment of a Naloxone access law containing the three significant provisions (NAL 3, 5, and 6) results in an increase in overdose death rates by 11 per 100,000 population. This simple calculation indicates that, compared to a supply side policy, the overall effect of a Naloxone access law on opioid overdose death rates is much higher, however, in the opposite of the intended direction.

Spatial econometrics has an important role to play in research on drug epidemics (see

[39]These estimated results are available from the corresponding author upon request.

e.g., Partridge et al. (2012) for a general discussion of the importance of spatial econometrics).[40] Due to movement of opioid drugs and Naloxone across state borders, in this paper, we demonstrate that the use of conventional, non-spatial analyses may be biased in this environment. Overall, due to a statistically significant spatial autoregressive component, the opioid overdose death rate in one state is associated with opioid overdose death rates in its neighboring states. This result means that there are spillover effects in opioid overdose death rates among neighboring regions (states). An increasing trend in opioid overdose death rates in one particular state may be followed by neighboring states as well.

Naloxone as a harm reduction strategy works well by reversing overdoses and saving lives. To combat opioid overdose deaths, however, Naloxone access laws do not appear to be a suitable strategy. The fight against opioid overdose rates requires policy makers to focus on dealing with opioid addiction and find ways to treat addiction. State-level enactment of a Naloxone access law can be viewed as a starting point to a strategy of implementing and expanding access to save lives, but not as a sufficient response to the opioid crisis and overdose problems. In addition to enactment of access laws, both federal and state governments should consider the next steps such as policy recommendations presented by Clark 2017 (e.g. team-based care model, more collaboration with pharmacists, expanding harm reduction treatment model, etc.). Both federal and state governments need to be involved in preventive policies more focused on regional rather than state-specific solutions.

The combination of Naloxone access law and increasing availability of high potency drugs could be partially responsible for not finding a significant result within the states that pass such a law (Doleac and Mukherjee, 2018). We are not able to control for an accurate measurement of opioid potency, but studies suggest opioid users shift toward consuming stronger, more illicit drugs like heroin and synthetic opioids like fentanyl when policies are enacted limiting opioid misuse (Gladden, 2016; Alpert et al., 2018; Evans et al., 2018; Jones et al., 2018).[41] There are two channels to explain this shift: less availability of prescription painkillers and drug users seeking out a stronger high.[42] In addition, cross border movement of Naloxone may influence our results for the direct effects of access laws.

Our results are broadly consistent with Doleac and Mukherjee (2018), who pointed out that while broadening Naloxone access increases opioid-related emergency room visits and opioid-related theft, it does not reduce overdose deaths. Conversely, while Rees et al. (2017) showed that heroin related overdose deaths are not associated with Naloxone access laws, they provide support for a protective effect of Naloxone access laws on overall drug-related deaths. We contribute to this literature by showing that Naloxone access has regional effects. Failing to control for spillover effects across state borders likely biases results.

We recognize several limitations in our research. First, many states have only recently enacted Naloxone access laws. Our data cover years 1999 to 2016, for those 19 states with newly enacted laws in 2015 and 2016, we do not have post implementation data. Empirical results may change with more post implementation data for these 19 states. Second,

[40]For more information, please refer to Gibbons and Overman (2012), McMillen (2012), and Corrado and Fingleton (2012).

[41]For more information, please refer to: https://www.vox.com/science-and-health/2017/5/8/15454832/fentanyl-carfentanil-opioid-epidemic.

[42]For more information, please refer to: https://www.vox.com/science-and-health/2017/8/3/16079772/opioid-epidemic-drug-overdoses.

a county level analysis would be preferable to assess the spillover effects across states, but these data were not consistently and publicly available for overdose death rates.[43]

One future avenue of research is to employ a mechanism that differentiates the relationship between neighbors by whether or not they have an access law. Our analysis does not differentiate between these types of neighboring states and this distinction may be important in determining the magnitude of the spillover effect. Further research should also consider applying a hierarchical analysis and provide spillover estimates at both levels of the hierarchy (including both county and state level data in county level model). Finally, research should examine the enactment of Naloxone access laws in conjunction with other policy responses, such as increased intervention and treatment programs for addiction to assess the impact of multiple policies on overdose death rates as well to limit the unintended consequences of Naloxone access on risky drug behaviors.

REFERENCES

Alpert, Abby, David Powell, and Rosalie Liccardo Pacula. (2018) "Supply-side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-deterrent Opioids," *American Economic Journal: Economic Policy*, 10, 1–35.

Beheshti, Annahita, Landyn Lucas, Tanika Dunz, Maryna Haydash, Hope Chiodi, Breanna Edmiston, Chad Ford, Natalie Bohn, John Hunter Stein, Anthony Berrett, et al.. (2015) "An Evaluation of Naloxone Use for Opioid Overdoses in West Virginia: A Literature Review," *American Medical Journal*, 6, 9.

Buchmueller, Thomas C and Colleen Carey. (2018) "The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Medicare," *American Economic Journal: Economic Policy*, 10, 77–112.

Chagas, André LS, Carlos R Azzoni, and Alexandre N Almeida. (2016) "A Spatial Difference-in-differences Analysis of the Impact of Sugarcane Production on Respiratory Diseases," *Regional Science and Urban Economics*, 59, 24–36.

Chan, Tat Y, Barton H Hamilton, and Nicholas W Papageorge. (2015) "Health, Risky Behaviour and the Value of Medical Innovation for Infectious Disease," *Review of Economic Studies*, 83, 1465–1510.

Chen, Zhenhua and Kingsley E Haynes. (2015) "Public Surface Transportation and Regional Output: A Spatial Panel Approach," *Papers in Regional Science*, 94, 727–751.

Clark, Michele N. (2017) *Qualitative Study of Opioid Overdose Education and Naloxone Access Strategies in Community Health Center Primary Care Settings: Opportunities for Expanding Access and Saving Lives.* PhD thesis, Boston University.

Coffin, Phillip O, Crystal Fuller, Liza Vadnai, Shannon Blaney, Sandro Galea, and David Vlahov. (2003) "Preliminary Evidence of Health Care Provider Support for Naloxone Prescription as Overdose Fatality Prevention Strategy in New York City," *Journal of Urban Health*, 80, 288–290.

Coffin, Phillip O and Sean D Sullivan. (2013) "Cost-effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal in Russian Cities," *Journal of Medical Economics*, 16, 1051–1060.

[43]For example, the CDC does not publish county level observations with less than nine overdose deaths.

Cohen, Alma and Liran Einav. (2003) "The Effects of Mandatory Seat Belt Laws on Driving Behavior and Traffic Fatalities," *Review of Economics and Statistics*, 85, 828–843.

Davis, Corey. (2015) "Naloxone for Community Ppioid Overdose Reversal," *Public Health Law Research*, 25.

Davis, Corey and Derek Carr. (2017) "State Legal Innovations to Encourage Naloxone Dispensing," *Journal of the American Pharmacists Association*, 57, S180–S184.

Davis, C and S Chang. (2013) "Legal Interventions to Reduce Overdose Mortality: Naloxone Access and Overdose Good Samaritan Laws," *The Network for Public Health Law*, 32, 2.

Davis, Corey, S Chang, and D Carr. (2017) "Legal Interventions to Reduce Overdose Mortality: Naloxone Access and Overdose Good Samaritan Laws," *Network for Public Health Law*.

Davis, Corey, Damika Webb, and Scott Burris. (2013) "Changing Law from Barrier to Facilitator of Opioid Overdose Prevention," *Journal of Law, Medicine & Ethics*, 41, 33–36.

Davis, Corey S and Derek Carr. (2015) "Legal Changes to Increase Access to Naloxone for Opioid Overdose Reversal in the United States," *Drug and Alcohol Dependence*, 157, 112–120.

Davis, Corey S, Sarah Ruiz, Patrick Glynn, Gerald Picariello, and Alexander Y Walley. (2014) "Expanded Access to Naloxone among Firefighters, Police Officers, and Emergency Medical Technicians in Massachusetts," *American Journal of Public Health*, 104, e7–e9.

de Andrade, Luiza Cardoso. (2016) *Spillover Effects of Blacklisting Policy in the Brazilian Amazon*. PhD thesis, Universidade de São Paulo.

Debarsy, Nicolas, Cem Ertur, and James P LeSage. (2012) "Interpreting Dynamic Space–time Panel Data Models," *Statistical Methodology*, 9, 158–171.

Delgado, Michael S and Raymond JGM Florax. (2015) "Difference-in-differences Techniques for Spatial Data: Local Autocorrelation and Spatial Interaction," *Economics Letters*, 137, 123–126.

Doleac, Jennifer L and Anita Mukherjee. (2018) "The Moral Hazard of Lifesaving Innovations: Naloxone Access, Opioid Abuse, and Crime," .

Dubé, Jean, Diègo Legros, Marius Thériault, and François Des Rosiers. (2014) "A Spatial Difference-in-differences Estimator to Evaluate the Effect of Change in Public Mass Transit Systems on House Prices," *Transportation Research Part B: Methodological*, 64, 24–40.

Elhorst, J Paul. (2014) *Spatial Econometrics: From Cross-sectional Data to Spatial Panels*. Springer.

Enteen, Lauren, Joanna Bauer, Rachel McLean, Eliza Wheeler, Emalie Huriaux, Alex H Kral, and Joshua D Bamberger. (2010) "Overdose Prevention and Naloxone Prescription for Opioid Users in San Francisco," *Journal of Urban Health*, 87, 931–941.

Evans, William N, Ethan Lieber, and Patrick Power. (2018). "How the Reformulation of OxyContin Ignited the Heroin Epidemic," National Bureau of Economic Research: .

Galea, Sandro, Jennifer Ahern, David Vlahov, Phillip O Coffin, Crystal Fuller, Andrew C Leon, and Kenneth Tardiff. (2003) "Income Distribution and Risk of Fatal Drug Overdose in New York City Neighborhoods," *Drug and Alcohol Dependence*, 70, 139–148.

Gatti, Uberto, Richard E Tremblay, and Hans MA Schadee. (2007) "Community Characteristics and Death by Homicide, Suicide and Drug Overdose in Italy: The Role of Civic Engagement," *European Journal on Criminal Policy and Research*, 13, 255–275.

Getis, Arthur. (2007) "Reflections on Spatial Autocorrelation," *Regional Science and Urban*

Economics, 37, 491–496.

Gladden, R Matthew. (2016) “Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid-involved Overdose Deaths27 states, 2013–2014,” *Morbidity and Mortality Weekly Report*, 65.

Green, Traci C, Emily F Dauria, Jeffrey Bratberg, Corey S Davis, and Alexander Y Walley. (2015) “Orienting Patients to Greater Opioid Safety: Models of Community Pharmacy-based Naloxone.,” *Harm Reduction Journal*, 12, 25–25.

Green, Traci C, Robert Heimer, and Lauretta E Grau. (2008) “Distinguishing Signs of Opioid Overdose and Indication for Naloxone: An Evaluation of Six Overdose Training and Naloxone Distribution Programs in the United States,” *Addiction*, 103, 979–989.

Griffith, Daniel A. (2005) “Effective Geographic Sample size in the Presence of Spatial Autocorrelation,” *Annals of the Association of American Geographers*, 95, 740–760.

Hembree, C, Sandro Galea, Jennifer Ahern, Melissa Tracy, T Markham Piper, J Miller, David Vlahov, and Kenneth J Tardiff. (2005) “The Urban Built Environment and Overdose Mortality in New York City Neighborhoods,” *Health & Place*, 11, 147–156.

Inocencio, Timothy J, Norman V Carroll, Edward J Read, and David A Holdford. (2013) “The Economic Burden of Opioid-Related Poisoning in the United States,” *Pain Medicine*, 14, 1534–1547.

Jaffe, Adam B. (1989) “Real Effects of Academic Research,” *American Economic Review*.

Jaffe, Adam B, Manuel Trajtenberg, and Rebecca Henderson. (1993) “Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations,” *Quarterly Journal of Economics*, 108, 577–598.

Jones, Christopher M, Emily B Einstein, and Wilson M Compton. (2018) “Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016,” *Journal of the American Medical Association*, 319, 1819–1821.

Keyes, Katherine M, Magdalena Cerdá, Joanne E Brady, Jennifer R Havens, and Sandro Galea. (2014) “Understanding the Rural-urban Differences in Nonmedical Prescription Opioid Use and Abuse in the United States,” *American Journal of Public Health*, 104, e52–e59.

Lakdawalla, Darius, Neeraj Sood, and Dana Goldman. (2006) “HIV Breakthroughs and Risky Sexual Behavior,” *Quarterly Journal of Economics*, 121, 1063–1102.

LeSage, James P and Kelley Pace. (2009) *Introduction to Spatial Econometrics*. Taylor & Francis Group, LLC.

Lim, Jamie K, Jeffrey P Bratberg, Corey S Davis, Traci C Green, and Alexander Y Walley. (2016) “Prescribe to Prevent: Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists,” *Journal of Addiction Medicine*, 10, 300.

McClellan, Chandler, Barrot H Lambdin, Mir M Ali, Ryan Mutter, Corey S Davis, Eliza Wheeler, Michael Pemberton, and Alex H Kral. (2018) “Opioid-overdose Laws Association with Opioid Use and Overdose Mortality,” *Addictive Behaviors*.

Nandi, Arijit, Sandro Galea, Jennifer Ahern, Angela Bucciarelli, David Vlahov, and Kenneth Tardiff. (2006) “What Explains the Association between Neighborhood-level Income Inequality and the Risk of Fatal Overdose in New York City?,” *Social Science & Medicine*, 63, 662–674.

National Research Council. (2004) *Indicators for Waterborne Pathogens*. National Academies Press.

Open Society Foundation. (2017) *Naloxone: Frequently Asked Questions.* http://naloxoneinfo.org/sites/default/files/Frequently%20Asked%20Questions-Naloxone_EN.pdf. Accessed on 01/16/2017.

Partridge, Mark D, Marlon Boarnet, Steven Brakman, and Gianmarco Ottaviano. (2012) "Introduction: Whither Spatial Econometrics?," *Journal of Regional Science*, 52, 167–171.

Rees, Daniel I, Joseph J Sabia, Laura M Argys, Joshua Latshaw, and Dhaval Dave. (2017). "With a Little Help from my Friends: The Effects of Naloxone Access and Good Samaritan Laws on Opioid-related Deaths," National Bureau of Economic Research: Cambridge, MA.

Richardson, Robin, Thomas Charters, Nicholas King, and Sam Harper. (2015) "Trends in Educational Inequalities in Drug Poisoning Mortality: United States, 1994–2010," *American Journal of Public Health*, 105, 1859–1865.

Rossen, Lauren M, Diba Khan, and Margaret Warner. (2013) "Trends and Geographic Patterns in Drug-poisoning Death Rates in the US, 1999–2009," *American Journal of Preventive Medicine*, 45, 19–25.

Rowe, Christopher, Glenn-Milo Santos, Eric Vittinghoff, Eliza Wheeler, Peter Davidson, and Philip O Coffin. (2016) "Neighborhood-Level and Spatial Characteristics Associated with Lay Naloxone Reversal Events and Opioid Overdose Deaths," *Journal of Urban Health*, 93, 117–130.

Rudd, Rose A, Noah Aleshire, Jon E Zibbell, and R Matthew Gladden. (2016) "Increases in Drug and Opioid Overdose Deaths - United States, 2000–2014," *American Journal of Transplantation*, 16, 1323–1327.

Ruhm, Christopher J. (2016) "Drug Poisoning Deaths in the United States, 1999–2012: A Statistical Adjustment Analysis," *Population Health Metrics*, 14, 2.

Salsberg, Robert. (2015) *Workers Comp Programs Fight Addiction among Injured Workers.* https://apnews.com/ccea326c84b747cdb1d7bff83efdb303/workers-comp-programs-fight-addiction-among-injured-workers. Accessed on 07/06/2017.

Scott, Greg, Sandra D Thomas, Harold A Pollack, and Bradley Ray. (2007) "Observed Patterns of Illicit Opiate Overdose Deaths in Chicago, 1999–2003," *Journal of Urban Health*, 84, 292–306.

Seal, Karen H, Robert Thawley, Lauren Gee, Joshua Bamberger, Alex H Kral, Dan Ciccarone, Moher Downing, and Brian R Edlin. (2005) "Naloxone Distribution and Cardiopulmonary Resuscitation Training for Injection Drug Users to Prevent Heroin Overdose Death: A Pilot Intervention Study," *Journal of Urban Health*, 82, 303–311.

Shah, Nina G, Sarah L Lathrop, Janet E Flores, and Michael G Landen. (2012) "The Influence of Living along the US-Mexico Border on Unintentional Drug Overdose Death, New Mexico (USA), 2005–2009," *Drug and Alcohol Dependence*, 125, 19–26.

Siegler, Anne. (2015) *Effect of the New York City Overdose Prevention Program on Unintentional Heroin-related Overdose Death, 2000-2012.* City University of New York.

Stobbe, Mike. (2017) *Soaring Overdose Death Rates Cut US Life Expectancy for 2nd Year.* https://apnews.com/a39695987f08449291ec3f671da9122d/Soaring-overdose-deaths-cut-US-life-expectancy-for-2nd-year. Accessed on 12/25/2017.

Sunak, Yasin and Reinhard Madlener. (2014) "Local Impacts of Wind Farms on Property Values: A Spatial Difference-in-differences Analysis," *FCN Working Paper.*

Tobler, Waldo R. (1970) "A Computer Movie Simulating Urban Growth in the Detroit Region," *Economic Geography*, 46, 234–240.

Unick, George, Daniel Rosenblum, Sarah Mars, and Daniel Ciccarone. (2014) "The Relationship between US Heroin Market Dynamics and Heroin-related Overdose, 1992–2008," *Addiction*, 109, 1889–1898.

Varga, Attila. (1998) "Local Academic Knowledge Spillovers and the Concentration of Economic Acitivity," *Regional Research Institute, West Virginia University, Research Paper 9803*.

Visconti, Adam J, Glenn-Milo Santos, Nikolas P Lemos, Catherine Burke, and Phillip O Coffin. (2015) "Opioid Overdose Deaths in the City and County of San Francisco: Prevalence, Distribution, and Disparities," *Journal of Urban Health*, 92, 758–772.

Walley, Alexander, Ziming Xuan, Holly Hackman, Emily Quinn, Maya Doe-Simkins, Amy Sorensen-Alawad, Sarah Ruiz, and Al Ozonoff. (2013) "Opioid Overdose Rates and Implementation of Overdose Education and Nasal Naloxone Distribution in Massachusetts: Interrupted Time Series Analysis," *British Medical Journal*, 346, 1–13.

Wheeler, Eliza, Peter J Davidson, T Stephen Jones, and Kevin S Irwin. (2012) "Community-based Opioid Overdose Prevention Programs Providing NaloxoneUnited States, 2010," *Morbidity and Mortality Weekly Report*, 61, 101.