1-29-2018

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

Elham Erfanian
West Virginia University, elhamerfanian@mix.wvu.edu

Alan R. Collins
West Virginia University, alan.collins@mail.wvu.edu

Daniel Grossman
West Virginia University, Daniel.Grossman@mail.wvu.edu

Regional Research Institute
West Virginia University

Working Paper Series

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

Elham Erfanian, Ph.D. Candidate, Division of Resource Economics and Management, Regional Research Institute, West Virginia University, Morgantown, WV 26506-6108, elhamerfanian@mix.wvu.edu;
Alan R. Collins, Professor and Assistant Director, Division of Resource Economics and Management, School of Natural Resources, West Virginia University, Morgantown, WV;
Daniel Grossman, Professor, Department of Economics, West Virginia University, Morgantown, WV

Working Paper Number 2018-03

Website address: rri.wvu.edu

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

Elham Erfanian*[1], Alan R. Collins†[1] and Daniel Grossman‡[1]
[1]West Virginia University - WVU

January 23, 2018

Abstract

Opioid overdose is the leading cause of unintentional death in the U.S. Narcan TM (Naloxone) is a prescription medicine that can reverse overdose effects. This research investigates the effect of Naloxone access laws on overdose death rates using state and temporal variation in the enactment of these laws. We also explore possible spillover effects between Naloxone access laws and overdose death rates across states. Our analyses reveal that when broken down by access law provisions, there exists a mixture of positive and negative effects on overdose death rates depending upon the provision. The results indicate that Naloxone access provisions have regional impacts by influencing overdose death rates within the state enacted and have a spillover effect in neighboring states. The magnitude of spillover effects is larger than direct effects in the states. Looking across multiple provisions, our findings provide no statistical evidence that these laws reduce opioid death rates.

Keywords: Opioid overdose death, Naloxone access law, Spatial spillovers
JEL Classification: I180, I120, C3

*elhamerfanian@mix.wvu.edu
†alan.collins@mail.wvu.edu
‡daniel.grossman@mail.wvu.edu

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. State response to the opioid crisis can be categorized by attempts to limit the supply of opioids through prescription drug monitoring programs and attempts to reduce the number of overdoses by authorizing the provision of drugs such as Naloxone (Davis and Chang (2013); Davis et al. (2013); Davis et al. (2014)). 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 addicts.

In this research, we estimate the effect of state level Naloxone access laws on overdose deaths using a spatial difference-in-differences framework. This analysis provides us with estimates of both within state and the spillover effects among contiguous states from enacting a Naloxone access law. The spillover analysis allows us to document biases of the standard model. We find that when Naloxone access laws are broken down by their provisions, a mixture of positive and negative impacts on opioid overdose death rates occurs, particularly within neighboring states. These results mean that state level adaptation of a Naloxone access law is associated primarily with either higher or lower opioid overdose deaths in neighboring states, and within the state itself. Thus, important spillover effects exist from the various provisions of Naloxone access laws on opioid overdose death rates.

Our main contribution to the literature is developing a SDID (Spatial Difference in Difference) 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 version 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[2]. 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 that the regional aspects of these laws has not been investigated.

The rest of the manuscript proceeds as follows. Section two provides background information on trends in opioid overdose and Naloxone access laws. Section three provides an empirical model and section four describes the data. In section five, we explain the method and spatial econometric framework. Section six reports the results and robustness checks. We conclude in section seven with a discussion and policy implications.

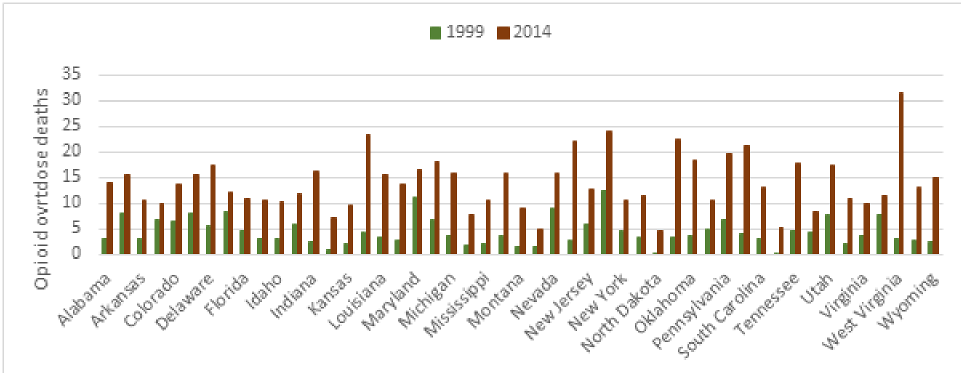
2 Background

2.1 Opioid Trends

Mortality from opioid overdose has more than quadrupled since 1999[3]. Figure 1 compares opioid overdose death rates among states in 1999 and 2014. Opioid overdose death rate increased during this time period in every state. In 2014, West Virginia had the highest rate of overdose death, while North Dakota had the lowest rate of overdose deaths. Between 1999 and 2014, increases in opioid overdose death rates ranged from 3.25 per 100,000 in California to 28.30 per 100,000 in West Virginia.

[1]For more information please refer to Rudd et al. (2016)
[2]Available at: http://lawatlas.org/
[3]Available at: https://www.cdc.gov/drugoverdose/epidemic/index.html

Figure 1: Opioid overdose death per 100,000, 1999 and 2014



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).[4]. Opiate overdoses can lead to depressed or slowed breathing, confusion, lack of oxygen to the brain, and possibly even death. Opioids have the potential for misuse even when prescribed for a legitimate reasons, such as a work-related injury.[5]

In 2015, 2.8 million private industry workers and 752,000 public sector workers suffered from nonfatal workplace injuries, many of which led to opioid receipt and potentially addiction and/or overdose (Salsberg, 2015).[6] Former Food and Drug Administration head David Kessler called the opioid epidemic one of the "great mistakes of modern medicine"[7]), workplace injuries were a driver for prescribing opioids that have the potential to transform into addiction and ultimately overdose and death.

Reducing opioid abuse and controlling overdose deaths is an important policy goal for both state and federal governments. For many years, opioid overdose prevention programs have provided protection services. Since 1996, an increasing number of community based programs have provided Naloxone (a non-controlled substance opioid[8]) to laypersons to reverse the effects of opioid overdose. Narcan TM (Naloxone) is a prescription medicine that can block the effects of opioids with no life threatening effects on the opiate users.[9] Naloxone acts on a person's brain by attaching to the same part of the brain that receive the opioid (Naloxoneinfo, 2017). Once administered, Naloxone takes two to three minutes for its effect to occur. If an overdose victim does not wake up, a second dose should be delivered.

Examples of Naloxone saving lives abound. For instance, Chad Ward, an Emergency Medical Services Supervisor in Huntington, WV noted that in 2015, there was 944 drug overdoses in Cabell County, which is 300% more than overdoses in 2014. By having access to Naloxone, Chad is able to save many patients.[10]. In another more famous example, the musician Prince suffered an oxycodone

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

[5]Available at: http://www.samhsa.gov/medication-assisted-treatment/treatment/opioid-overdose

[6]Available at: https://apnews.com/ccea326c84b747cdb1d7bff83efdb303/workers-comp-programs-fight-addiction-among-injured-workers

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

[8]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.

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

[10]Available at: http://www.wsaz.com/content/news/WSAZ-Investigates-A-Dose-of-Reality-368538771.html

overdose on April 15, 2016. After giving 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 .[11]

The examples above demonstrate the conflicting viewpoints of Naloxone. Whether Naloxone saves lives or simply delays overdose death is the paradox at the center of whether it is a solution to the overdose epidemic.[12] ,[13] ,[14] ,[15] That it may give a false sense of security to users makes Naloxone a prime example of a moral hazard issue in health economics.[16] Maine Governor, Paul LePage is among the most outspoken of Naloxone access opponents who believes by providing Naloxone to opioid users, they may be saved once, but they are just going to die later .[17]

With the growth in overdose deaths, interest in assessing the effects of Naloxone access laws and overdose prevention programs on overdose deaths has increased (e.g. Walley et al. (2013); Visconti et al. (2015). Adaption of the Naloxone access laws is associated with a 9 to 11 percent reduction in opioid- related deaths (Rees et al. (2017)). In another study, Siegler (2015) found a 16% decrease, but his results were not statistically significant for heroin-related overdose mortality in New York City after the implementation of overdose prevention program. Similarly, Rees et al. (2017) find statistically insignificant effects of the Naloxone access law on heroin-related deaths in the U.S.

No previous research has 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 the law are examined with the assumptions that an access law and overdose death rate in one state are totally independent of access laws and death rates in neighboring states. These assumptions ignore the effects of access laws on adjacent states which could be in a same direction or opposite.

2.2 Naloxone Access Laws

Naloxone has been available by prescription since 1996 although the legal environments for prescribing and dispensing Naloxone varies by state. State legislations have enacted a variety of provisions to expand and ease prescribing and distributing Naloxone to prevent overdoses. For example, a number of states have passed laws that involve less civil and criminal liability, whether for prescribers, dispensers or users (Lim et al. (2016)). The reasoning behind implementing these laws was to remove the barriers to Naloxone distribution and use. In some states, prescriptions of Naloxone can be authorized to third parties, while in other states, laypersons are immune from criminal and/or civil liability when administering Naloxone. Additional versions of the law remove criminal liability for possession of Naloxone. In some states prescribing by a standing order [18] is authorized while in other states it is not.

The list below provides our breakdown of Naloxone access law provisions into eleven types of provisions.

[11] Available at: https://www.cbsnews.com/news/official-pills-found-at-princes-estate-contained-fentanyl/

[12] Available at: https://www.nytimes.com/2017/05/09/us/opioids-narcan-drug-overdose-heroin-fentanyl.html?emc=eta1

[13] Available at: http://www.wsaz.com/content/news/WSAZ-Investigates-A-Dose-of-Reality-368538771.html

[14] Available at: https://www.cbsnews.com/news/official-pills-found-at-princes-estate-contained-fentanyl/

[15] Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4675355/pdf/nihms742274.pdf

[16] Available at: https://www.nytimes.com/2016/07/28/us/naloxone-eases-pain-of-heroin-epidemic-but-not-without-consequences.html?emc=eta1

[17] Available at: http://www.huffingtonpost.com/entry/maine-governor-paul-lepage-heroin-addicts_us_5717ef01e4b0479c59d6e865

[18] A standing order is a physician's order that can be carried out by other health care workers when predetermined conditions have been met. Available at: http://naloxoneinfo.org/case-studies/standing-orders

NAL 1. Having a Naloxone access law

NAL 2. Having immunity from criminal prosecution for prescribing, dispensing or distributing Naloxone to a layperson for prescribers

NAL 3. Having immunity from civil liability for prescribing, dispensing or distributing Naloxone to a layperson for prescribers

NAL 4. Having immunity from professional sanctions for prescribing, dispensing or distributing Naloxone to a layperson for prescribers

NAL 5. Having immunity from criminal prosecution for prescribing, dispensing or distributing Naloxone to a layperson for dispensers

NAL 6. Having immunity from civil liability for prescribing, dispensing or distributing Naloxone to a layperson for dispensers

NAL 7. Having immunity from professional sanctions for prescribing, dispensing or distributing Naloxone to a layperson for dispensers

NAL 8. Third parties' authorization to prescribe Naloxone

NAL 9. Pharmacists are allowed to dispense or distribute naloxone without a patient- specific prescription from another medical professional.

NAL 10. Immunity from criminal liability when administering Naloxone for a layperson

NAL 11. Immunity from civil liability when administering Naloxone for a layperson

NAL 12. Removing criminal liability for possession of Naloxone

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 the Naloxone law passed starting from 2001. A total of 27 states and the District of Columbia adopted a Naloxone access law prior to 2015 with an additional 18 states adopting laws since 2015. Twenty-three of these states allowed "standing orders" (also called "non-patient-specific prescriptions") (Rees et al., 2017). Figure 2 shows the distribution of Naloxone access law at two points of time: 2001 and 2014. As shown in this figure, states with access laws by 2014 are concentrated on the east and west coasts. Table 2 demonstrates the effective years for different provisions of Naloxone access laws. For instance, while New Mexico was the first state to enact Naloxone access laws, they did not enact provisions authorizing standing order prescription or removing criminal liability for possession.

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); Green et al. (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 an overdose prevention tool in a nationwide and regional scale is still mixed. In this study, we employ state level analysis in the dates of enacting Naloxone access law to investigate the spillover effects of law enactment at the national level to investigate if there is any regional spillover effects in opioid overdose and the Naloxone access law enactment.

Table 1: Effective dates of Naloxone Access Laws, 1999-2014

State	Naloxone Access Law effective date
California	January 1, 2008
Colorado	May 10, 2013
Connecticut	October 1, 2003
Washington, D.C.	March 19, 2013
Delaware	August 4, 2014
Georgia	April 24, 2014
Illinois	January 1, 2010
Kentucky	June 25, 2013
Maine	April 29, 2014
Maryland	October 1, 2013
Massachusetts	August 2, 2012
Michigan	October 14, 2014
Minnesota	May 10, 2014
New Jersey	July 1, 2013
New Mexico	April 3, 2001
New York	April 1, 2006
North Carolina	April 9, 2013
Ohio	March 11, 2014
Oklahoma	November 1, 2013
Oregon	June 6, 2013
Pennsylvania	November 29, 2014
Rhode Island	June 18, 2012
Tennessee	July 1, 2014
Utah	May 13, 2014
Vermont	July 1, 2013
Virginia	July 1, 2013
Washington	June 10, 2010
Wisconsin	April 9, 2014

Note: Alabama, Alaska, Arkansas, Florida, Hawaii, Idaho, Indiana, Iowa, Louisiana, Mississippi, Nebraska, New Hampshire, Nevada, North Dakota, South Carolina, South Dakota, Texas, and West Virginia have adopted Naloxone access laws since 2014.

Figure 2: Naloxone Access Law in 2001 and 2014

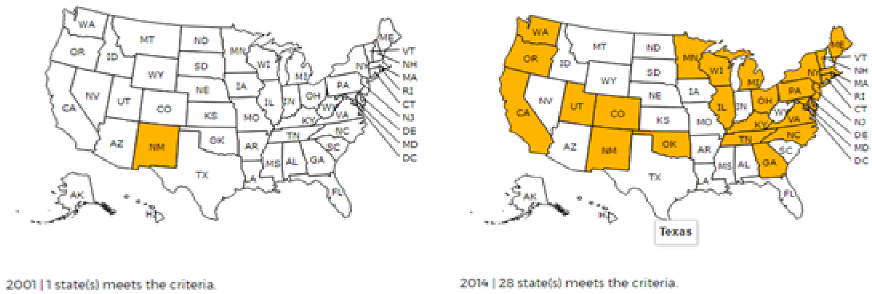


Table 2: Effective dates of Naloxone Access Law Provisions, 1999-2014

Year	NL2	NL3	NL4	NL5	NL6	NL7	NL8	NL9	NL10	NL11	NL12
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	

3 Empirical Models

Empirical studies have shown that a number of factors influence opioid overdose deaths in the U.S. Despite 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. Table 3 shows the important variables, study region, their impact on overdose deaths and the reference.

Table 3: Effective dates of Naloxone Access Law Provisions, 1999-2014

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

The difference-in-difference (DID) technique is an econometric tool first applied in the 19th century to control for before-and-after implementation of a treatment or policy [19] (National Research Council and others, 2004; Branas et al., 2011; Morris et al., 2014; Dimick and Ryan, 2014 are examples of health-related research that have applied a DID analysis). A standard DID model to evaluate the effects of a Naloxone access law by differentiating between treatment and control (untreated) states is represented by:

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

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

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 such as: presence of a medical marijuana law, quantities of drug prescription, amount of heroin related crime, high-injury and risky occupations, population density, income inequality, uninsured rate, college attainment rate, spending on education, unemployment rate, and poverty rate. $NAL_{it}T_{it}$ 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. 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 state's 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 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)). They are independent points and therefore there is no correlation between them and their neighbors. However, LeSage and Pace (2009) explain the case of spatial dependency: "In contrast to point observations, for a region we rely on the coordinates of an interior point representing the center (the centroid). An important point is that in spatial regression models each observation corresponds to a location or region". 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 most cases, this assumption is not applicable and observations located at different points or regions are dependent (LeSage and Pace (2009). Suppose we have two regions (neighbors) i and j. If these two regions are spatially correlated and normality for 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 variety of units of measurement for spatial dependency such as neighbors, distance, and links (Getis (2007)). 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 a weight matrix for neighbors with border touching seems intuitively appealing.

The use of spatial difference-in-difference (SDID) models has gained attraction in urban economics in recent years (Dubé et al. (2014); Sunak and Madlener (2014); Hembree et al. (2005)). However, to the best of our knowledge few studies perform SDID model in public health and public policy research (Andrade (2016); Chagas et al. (2016)) are noted exceptions). We argue that opioid overdose death rates and Naloxone access laws need to be assessed within a regional framework.

For example, adaptation of a policy in one state could be followed by surrounding states as well. Marijuana legalization status in U.S. states is a good example of mimicking law enactment in neighboring states. In such cases, not only would the variable of interest be affected by its own control variables, but it also may be affected by its neighbors' control variables.

The medication (in our case Naloxone) can be transferred across state borders. In this case, even though in one state there is no Naloxone access law, users can buy Naloxone in a neighboring state and use it in their home state. This transmission of Naloxone could affect the opioid overdose death rates in neighboring states. The opioid epidemic in the U.S. is clustered in specific regions such as Appalachia and the Southwest [20], [21] (see Rudd et al. (2016)). Therefore, analyzing the effectiveness of the Naloxone access law on opioid overdose deaths needs to be investigated within a regional framework rather than a standard state level analysis.

When a spatial component (whether it be the spatial component of dependent variable, control variables or the error term) is statistically significant, the coefficients estimated by non-spatial models (in our case a general DID) would be biased. Also variances may be non-efficient (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 the spatial component to a non-spatial econometric analysis in a panel data framework. The general SDID model developed for opioid overdose death rate can be written as

$$
\begin{aligned}
TODDrate_{it} =& \alpha_0 + \alpha_1 NAL_{it}T_{it} + \sum \alpha_j X_{ijt} + \rho WTODDrate_{jt} + \vartheta WNAL_{jt}T_{jt} \\
&+ \theta W X_{jt} + \nu_i + \omega_t + \epsilon_{it}
\end{aligned} \tag{3}
$$

where $TODDrate$ stands for the opioid overdose deaths per 100,000 population in state i and time t, NAL represents a dummy variable whether the state has a Naloxone access law in a given year. X is a vector of demographic variables described above, while ν_i and ω_t are state and year fixed effects, respectively. The terms $WTODDrate$, $WNALT$, WX, and $W\epsilon$ denote the spatial components of opioid overdose death, Naloxone access law, other control variables, and the error term. ρ,ϑ,and θ represent the spillover effects of the dependent variable, independent variables, and the error term. They explain the effects of dependent variable, independent variables and error term of neighboring states j on the dependent variable in specific state i.

We examine the impact of Naloxone access laws with three different approaches. First, following Rees et al. (2017), we impose a dummy variable for passage of a Naloxone access law at the state level. For the second approach, we assess the impact of access laws by the number of days after effective date of the law. To allow for the effects of the law to change over time, a quadratic form of the days after the law enactment was included in this approach. By imposing the quadratic form of the days after law variable, we will be able to see whether or not the effect of the law is constant or diminishing over time. Finally, the third approach provides for a breakdown of access laws by their provisions. Since Naloxone access laws are not homogenous, to evaluate the effects of the law on opioid overdose deaths one needs to differentiate between the provisions included in each law.

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.,

[20] 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

[21] 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

2015). We expect to see positive and significant effects of availability of legal and illegal opioids on opioid overdose death rates. Medical marijuana laws should have a negative effect on opioid overdose death rates because we expect opioids and marijuana to be substitutes. Laws allowing medical marijuana will likely reduce the cost of receiving marijuana and therefore decrease the quantity demanded of opioids.

4 Data

Data for constructing the model come from a number of different sources. We use data from CDC Wonder for 1999-2014 [22] which contain the universe of overdose deaths and 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. 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 include deaths coded as unintentional (X40–44), homicide (X85), undetermined intent (Y10–Y14), and suicide cases (X 60–64).[23] 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).

For our variable of interest, we create measures of whether the state had a Naloxone law, the various provisions of each law, and effective dates from the Prescription Drug Abuse Policy System (PDAPS).[24] For control variables in the X vector, Unick et al. (2014) recommend including illicit drug price. Without having 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 came from controlled substances transactions of prescriptions available through Automated Reports and Consolidated Ordering System (ARCOS).[25]

State level economic variables such as per pupil spending on education, poverty rate, unemployment rate as well as population density and uninsured rate were obtained from U.S. Census Bureau. Income inequality, high school attainment, and the college attainment data were obtained from the U.S. state-level income inequality data and annual state-level measures of human capital attainment at Mark W. Frank home page.[26] Per capita personal income was based on the information provided by Federal Reserve Bank of ST. Louis (FRED).[27] Employment in mining, construction, and manufacturing and labor force are collected from Bureau of Labor Statistics (BLS).[28] Medical marijuana law was collected from the leading source for pros and cons of controversial issues.[29] Finally, the spatial weight matrix - the 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 Dis-

[22] National Vital Statistics System (NVSS)

[23] As a robustness check we test the total number of opioid overdose deaths as the dependent variable (not restricted to ICD-10 codes).

[24] Available at: http://pdaps.org/

[25] Available at: https://www.deadiversion.usdoj.gov/arcos/retail_opioid_summary/

[26] Available at: http://www.shsu.edu/eco_mwf/inequality.html

[27] Available at: https://fred.stlouisfed.org/release?rid=151

[28] Available at: https://www.bls.gov/sae/data.htm

[29] Available at: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881

trict of Colombia were included in our analysis. In spatial analysis, continuity 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 (Tobler (1970)). Descriptive statistics for each variable are reported in table 4 along with the expect signs of Naloxone access law and control variables. Following previous studies (Rees et al. (2017)) which found the negative effect of the Naloxone access law on opioid overdose deaths, we expect to have a negative effects of the law on opioid overdose death rates.

5 Methods

5.1 Exploring spatial dependency in opioid overdose death rates across states

As we mentioned in previous section, the economic distance concept is a motivation for spatial spillover effects. Before analyzing spatial dependency by corresponding econometrics models, an intuitive way to identify clusters is by looking at the map of the overdose death rates. Figure 3 shows the map of opioid overdose death rates for 1999 and 2014.

Opioid overdose death rates have increased over time. In 1999, only two states had an overdose death rate between 8-10 percent. By 2014, 33 states had an overdose death rate between 8-30 percent. Also, some spatial clusters are obvious especially in 2014. New Mexico had the highest opioid overdose death rate in 1999. In 2014, its surrounding states also had high rates of overdose deaths. Substantial clustering also exists 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 rate across neighboring states. A common index to find out the spatial autocorrelation is the Global Moran's I index.[30] As pointed out by Chen and Haynes (2015), Moran's I is a test on a yearly base. A significant and positive z-value for Moran's I index implies a positive spatial autocorrelation. Table 4 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 is a significant spatial autocorrelation among state level opioid overdose death rate in the U.S. This means the U.S. opioid overdose death rate 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 local Moran's I test (LISA). Scatter plots of LISA shows observations in four different quadrants: High value observation surrounded by high value observations (i.e. QI: HH) and 3 other clustering for LH (QII), HL (QIV), and LL (QIII) quadrants. Figure 4 provides Moran scatter plots of the US opioid overdose death rates in 1999 and 2014. This figure illustrates that in both years, most of the states with high overdose rate are surrounded by states with high overdose rates. This also is true for the states with low overdose death rates. Thus, we apply a first-order contiguity weight matrix.

The existence of statistically significant spatial autocorrelation among states implies that the ordinary least square estimations (non-spatial models) may lead toward biased estimates of the regression results. 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)[31] is

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

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

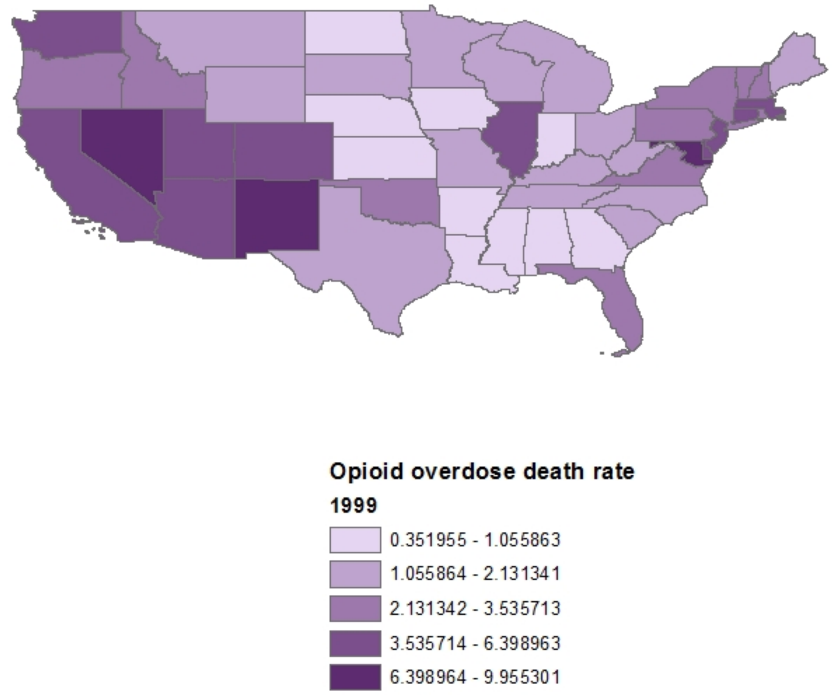
Table 4: Descriptive Statistics

Variable	Mean	Standard Deviation	Min	Max	Expected sign of coefficient
Opioid overdose death rates (per 100K pop)	6.30	4.08	0.15	29.94	
Total opioid overdose death rates (per 100K pop)	6.62	4.30	0.15	32.12	
NAL 1	0.090	0.274	0	1	-
NAL 2	0.051	0.213	0	1	-
NAL 3	0.052	0.213	0	1	-
NAL 4	0.024	0.142	0	1	-
NAL 5	0.047	0.206	0	1	-
NAL 6	0.048	0.208	0	1	-
NAL 7	0.023	0.139	0	1	-
NAL 8	0.061	0.229	0	1	-
NAL 9	0.022	0.133	0	1	-
NAL 10	0.051	0.209	0	1	-
NAL 11	0.040	0.183	0	1	-
NAL 12	0.008	0.086	0	1	-
Days after Naloxone access law (days/1000)	0.142	0.573	0	5.015	-
Square of the days after Naloxone access law (days/1000)	349	1,978	0	25,150	+
Presence of Medical marijuana law	0.21	0.41	0	1	-
Heroin arrest rate (arrests/100k pop)	139.57	105.82	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)	338.50	1,221.79	5.028	9,655.19	-/+
Income inequality (Income share for the top %10) (%)	44.44	4.90	33.27	62.17	
College attainment (the total number of college graduates/ the total state population) (%)	0.19	0.04	0.10	0.45	-
Spending on education ($1000)	9.22	2.83	4.16	20.60	-
Poverty rate (%)	13.30	3.37	5.60	23.90	+
Unemployment rate (%)	5.82	2.06	2.30	13.70	+
Uninsured rate (%)	13.23	3.97	3.00	26.10	+
Median HH income (Thousand dollars)	47.15	8.36	29.29	76.16	-
Per capita income (Thousand dollars)	36.81	8.45	20.56	70.46	-
Number of observations			784		

Table 5: Moran's I index for U.S. opioid overdose death rate

	1999	2014
Moran's I	0.407	0.329
z-statistics	5.413	3.842
p-value	0.01	0.01

Figure 3: Opioid overdose death rates in the U.S. 1999 and 2014



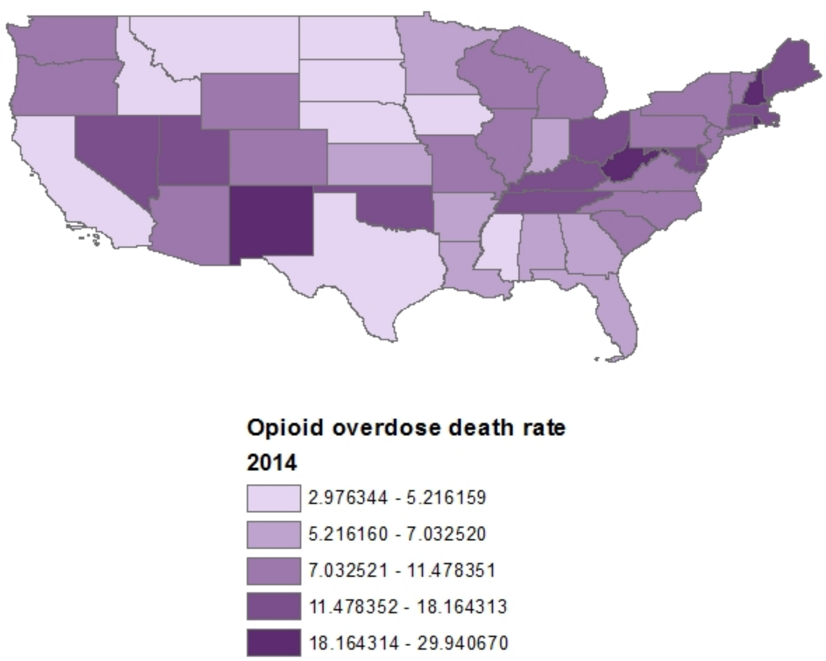
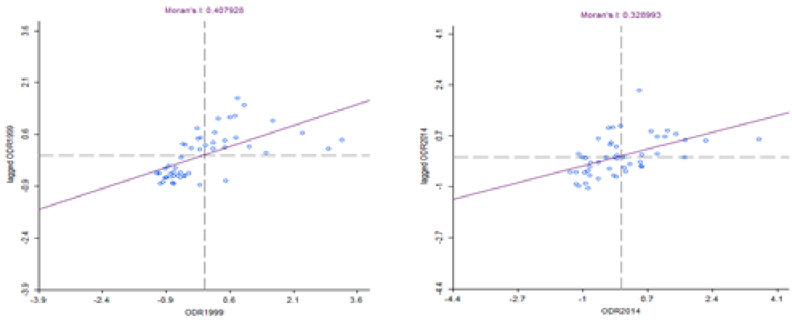


Figure 4: Moran's i scatter plot of U.S. state's opioid overdose death rates (1999 and 2014)



violated. A SUTVA violation means that in determining the treatment effect, considering one's 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 of which is the spatial autoregressive lag model (SAR) as shown in equation (3). Second, a Spatial Error Model (SEM) assumes dependency in error term. SLX model or spatial lag of control variable assumes the control variables could 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 reasons to suspect that the spatial spillovers are important both theoretically and empirically when studying the effect of access policy both with state and temporal variation. To evaluate the effects of the 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. In both cases, the spatial models were the appropriate specification [32] (LM for non-spatial against SAR = 89.8 and P-value = 0.00, LM for non-spatial against SEM = 39.3 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 (LMLAG[33] = 91.47 > LMERROR[34] = 40.99). Knowing that the SAR, SEM, and SLX models are nested within SDM and SDEM and for applied works LeSage recommends applying either a SDM or SDEM[35] , we continue our estimations by focusing on SDM model which is a global spatial econometric model encompassing both SAR and SLX models.

6 Spatial Results

As discussed in the previous sections, 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 good for several reasons. First, we need the weight matrix to be exogenous to

[32]For more information please refer to Florax et al. (2003)
[33]LMLAG stands for LM spatial lag
[34]LMERROR stands for LM spatial error
[35]For more information please refer to LeSage (2014)

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); Attila (2000), Chagas et al. (2016)).

Table 6 presents the spatial regressions results for Models 1 and 2 as discussed in section 3. Within these two models, there are no statistically significant direct effects of access laws on overdose death rates. Indirect effects 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.

Table 6: Estimation results for two models of access laws: dummy (NAL 1), days after passage of access law

Determinants	Model 1		Model 2	
	Direct	Indirect	Direct	Indirect
Naloxone access law 1	0.049	4.687***	-	-
	(0.894)	(0.000)		
Days after NAL 1 law	-	-	-0.56	3.270***
			(0.170)	(0.007)
Days after NAL 1 law ^{2}	-	-	0.0001	-0.0006**
			(0.233)	(0.062)
Medical marijuana law	0.415	1.175	0.509	1.534
	(0.230)	(0.195)	(0.152)	(0.123)
Heroin related arrest	0.006***	0.007	0.006***	0.006*
	(0.000)	(0.038)	(0.000)	(0.066)
Opioid prescription	0.011***	0.029	0.011***	0.029***
	(0.000)	(0.000)	(0.000)	(0.000)
Employment Ratio	48.511***	-58.280	44.024***	-56.75***
	(0.000)	(0.004)	(0.000)	(0.006)
Population density	-0.001	-0.001	-0.001	-0.001
	(0.170)	(0.732)	(0.352)	(0.826)
Income inequality index	0.011	-0.026	0.010	-0.015
	(0.780)	(0.788)	(0.801)	(0.872)
College graduate	-0.101	0.034	-0.087	0.039
	(0.101)	(0.808)	(0.150)	(0.782)
Education spending per student	0.127	-0.151	0.177	-0.095
	(0.324)	(0.614)	(0.183)	(0.756)
Poverty	-0.087	0.009	-0.095	0.075
	(0.525)	(0.977)	(0.495)	(0.822)
Unemployment	0.024	0.340	0.006	0.382
	(0.823)	(0.174)	(0.956)	(0.171)
Uninsured	0.004	0.062	0.000	0.032
	(0.927)	(0.578)	(0.988)	(0.780)
Per capita income	-3.688***	2.876	-3.500***	2.385
	(0.000)	(0.075)	(0.000)	(0.165)
ρ		0.26		0.27
		(0.000)		(0.000)
R^2		0.85		0.85
Observations		784		784

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

Model 3 differentiates between laws by breaking them down into their specific provisions and reveals more information about the impacts of laws by differentiating based upon provisions. 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.

The results in Table 7 reveal that the direct, indirect and total effects of the Naloxone access law are heterogeneous when we break down these laws by their provisions. The direct effect indicates the effects of the treatment status on own state opioid overdose death rate, and indirect effect shows the effects of provisions on surrounding states. Out of eleven provisions, five (immunity from professional sanctions for prescribers (NAL 4), immunity from professional sanctions for dispensers (NAL 7), third party authorizations (NAL 8), immunity from civil liability for layperson (NAL 11), and removing criminal liability for possession of naloxone without a prescription (NAL 12)) have statistically significant direct effects. Positive direct effects occur for NAL 4, NAL 11, and NAL 12 - meaning these provisions increase overdose death rates in the states where they are enacted. Negative direct effects (provisions decrease overdose death rates in states where enacted) are found for NAL 7 and 8.

Four provisions have significant indirect effects with the same sign as the direct effects (NAL 4, NAL 7, NAL 11, and NAL 12). In each case, indirect effects are much larger than direct effects, from 1.78 and 4.99 times greater than the corresponding direct effects. All provision variables with either a significant direct or indirect effect (NAL 4, NAL 7, NAL 8, NAL 10, NAL 11, and NAL 12) also have significant total effects. Thus, both positive and negative impacts are found to exist for Naloxone law provisions with spillover effects dominating the direct effects.

Other influences on opioid overdose death rates include heroin related arrests and opioid prescription with positive, statistically significant direct, indirect and total effects. Thus, more heroin related crime and prescription opioids in one state will increase the opioid overdose death rate both within that state as well as surrounding states. Employment of those who work at mining, construction and manufacture industries also increases opioid overdose death rates within the state, but decreases this rate in first order surrounding states.

Unemployment rate has positive and statistically significant indirect and total effects on opioid overdose death. The implication of these positive coefficients is that a higher unemployment rate in one state will increase opioid overdose death rates in surrounding states. Per capita income has statistically significant effects on opioid overdose death rates - negative direct and positive indirect effects. The implication is that increased per capita income in state i reduces opioid overdose death rate in state i, but increases death rate in neighboring j states. States with higher per capita incomes and population densities have lower opioid overdose death rates, while less urban states with lower per capita incomes suffer from higher opioid overdose death rate.

These results are consistent with Keyes et al. (2014), but contradict Gatti et al. (2007), whose research focused on Italy. In the Gatti and Tremblay study, the authors found drug overdose deaths were explained mainly by wealth. However, without an exact definition for the total number of deaths from drug overdose, the reason for discrepancy could be the definition of drug overdose. Also from Table 7, population density has a significant and negative direct and indirect effect on opioid overdose death rate. The implication of these negative coefficients is that a more dense area has less opioid overdose death rate both within the state and in adjacent states. College graduate rate has a negative and significant direct effect on opioid overdose death rate. Other variables (medical marijuana law, income inequality, education spending per student, poverty rate, and uninsured rate) do not have significant effects on overdose death rates.

Finally, to check the sensitivity of our results, 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

Table 7: Direct and indirect effects of SDM model (Based on Model 3)

Determinants	Direct effect	Indirect effect	Total effect
Naloxone access law 2	3.335	-0.322	3.012
	(0.481)	(0.978)	(0.832)
Naloxone access law 3	-1.774	6.429	4.655
	(0.715)	(0.596)	(0.744)
Naloxone access law 4	14.256***	25.337***	39.593***
	(0.000)	(0.004)	(0.000)
Naloxone access law 5	-0.115	2.778	2.662
	(0.970)	(0.730)	(0.776)
Naloxone access law 6	-2.233	-6.854	-9.087
	(0.516)	(0.444)	(0.397)
Naloxone access law 7	-10.862***	-21.315**	-32.178***
	(0.001)	(0.023)	(0.004)
Naloxone access law 8	-1.918***	-1.287	-3.206*
	(0.003)	(0.420)	(0.103)
Naloxone access law 9	-0.366	-0.170	-0.536
	(0.666)	(0.943)	(0.843)
Naloxone access law 10	-1.337	-3.426	-4.763*
	(0.108)	(0.145)	(0.097)
Naloxone access law 11	1.918***	6.469***	8.387***
	(0.016)	(0.008)	(0.003)
Naloxone access law 12	2.667***	12.981***	15.648***
	(0.015)	(0.000)	(0.000)
Medical marijuana law	0.077	0.177	0.255
	(0.816)	(0.837)	(0.804)
Heroin related arrest	0.004***	0.005	0.010***
	(0.000)	(0.116)	(0.006)
Opioid prescription	0.012***	0.028***	0.040***
	(0.000)	(0.000)	(0.000)
Employment Ratio	53.368***	-53.916***	-0.547
	(0.000)	(0.005)	(0.978)
Population density	-0.003**	-0.010*	-0.013**
	(0.027)	(0.062)	(0.026)
Income inequality index	0.045	-0.049	-0.004
	(0.248)	(0.583)	(0.965)
College graduate rate	-0.115*	0.052	-0.063
	(0.053)	(0.699)	(0.676)
Education spending per student	0.082	-0.060	0.022
	(0.515)	(0.829)	(0.943)
Poverty rate	-0.120	-0.152	-0.272
	(0.380)	(0.653)	(0.465)
Unemployment rate	0.140	0.648**	0.788***
	(0.213)	(0.014)	(0.004)
Uninsured rate	-0.020	-0.037	-0.058
	(0.655)	(0.741)	(0.662)
Per capita income	-3.540***	3.245**	-0.295
	(0.000)	(0.044)	(0.863)
ρ		0.23	
		(0.000)	
R^2		0.87	
Observations		784	

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

undetermined intent) (Ruhm (2016)). In robustness check the dependent variable is a comprehensive measure of opioid overdoses, which is rather similar to our limited opioid overdose death variable. The results of the estimation of equation 3 with the new dependent variable are reported in Table 7. These results are very similar in terms of statistical significance and coefficient signs for the Naloxone access law provisions compared to those in Table 7.

7 Conclusions

In this research, we examined the impact of Naloxone access laws enacted by state legislatures around the U.S. on opioid overdose deaths and their spillover effects to surrounding states. We applied spatial econometrics models to avoid potential bias in coefficients, which arises by ignoring spatial autocorrelation in ordinary least square models. Our regression results from all three models suggest that while some significant influences exist on overdose death rates within the state, spillover effects of access laws dominate in terms of magnitude – about four times larger than significant direct effects in Table 7. Thus, Naloxone access laws have more regional than state level effects.

Breaking down access laws by their provisions, our results show that enactment of a Naloxone access law effects opioid overdose death rates both within the state and in neighboring states. We find positive direct, indirect and total effects for law provisions that: provide immunity from professional sanction for prescriber, provide immunity from civil liability for layperson, and remove criminal liability for possession of Naloxone. These three provisions increase aggregate opioid related death rates both within the state and neighboring states. Based upon our results, these provisions do not help reduce opioid overdose death rates.

Conversely, three Naloxone access law provisions (i.e. immunity from professional sanction for dispenser, third parties' authorization to prescribe Naloxone, and immunity from criminal liability for a layperson administering Naloxone) have negative total effects, reducing opioid overdose death rates in aggregate, mainly within neighboring states. Immunity from professional sanction for dispenser decreases opioid overdose death rates within neighboring states. Also, provisions that remove criminal, rather than civil liabilities decrease overdose death rates.

It is useful to compare the magnitude of the aggregate effects from Naloxone access law provisions with the effects for heroin related arrests and drug prescriptions. To do that, we use the state level means to compare relative magnitudes. For example, if an overdose prevention policy could increase heroin arrests by 100% and reduce opioid prescriptions by 50%, the impact of this policy would reduce overdose death by 2.79 and 1.13 per 100,000 population, respectively. Conversely, the total effect of enactment of a Naloxone access law containing the three most common provisions (NAL 8, 10, and 11) results in a slight increase in the overdose death rate of 0.43 per 100,000 population.

Spatial econometrics has an important role to play in research on drug epidemics (see e.g., Partridge et al. (2012) for a general discussion of the importance of spatial econometrics).[36] We demonstrate in this paper use of conventional, non-spatial analyses are biased in this environment. Overall, due to a significant spatial autoregressive component, the opioid overdose death rate in one particular state is associated with opioid overdose death rates in neighboring states. This result means 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 and vice versa. Thus, opioid overdose death rates represent more a regional epidemic rather than a state level epidemic.

We relate the mixed positive and negative results of our research to the neo-classical economics

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

Table 8: Direct and indirect effects of SDM model for the unrestricted dataset (Based on Model 3)

Determinants	Direct effect	Indirect effect	Total effect
Naloxone access law 2	3.355	-3.926	-0.370
	(0.484)	(0.761)	(0.980)
Naloxone access law 3	-2.001	8.991	6.989
	(0.703)	(0.506)	(0.661)
Naloxone access law 4	14.764***	29.174***	43.938***
	(0.000)	(0.001)	(0.000)
Naloxone access law 5	-0.365	4.990	4.624
	(0.911)	(0.575)	(0.651)
Naloxone access law 6	-2.001	-8.430	-10.431
	(0.581)	(0.399)	(0.376)
Naloxone access law 7	-11.346***	-25.767**	-37.113***
	(0.001)	(0.010)	(0.002)
Naloxone access law 8	-2.098***	-1.897	-3.996*
	(0.002)	(0.261)	(0.057)
Naloxone access law 9	-0.478	-0.609	0.130
	(0.593)	(0.798)	(0.962)
Naloxone access law 10	-1.423	-3.662	-5.085*
	(0.115)	(0.145)	(0.094)
Naloxone access law 11	2.120***	7.305***	9.426***
	(0.014)	(0.005)	(0.002)
Naloxone access law 12	2.916***	12.845***	15.761***
	(0.009)	(0.000)	(0.000)
Medical marijuana law	0.077	0.177	0.255
	(0.816)	(0.837)	(0.804)
Heroin related arrest	0.004***	0.005	0.010***
	(0.000)	(0.116)	(0.006)
Opioid prescription	0.012***	0.028***	0.040***
	(0.000)	(0.000)	(0.000)
Employment Ratio	53.368***	-53.916***	-0.547
	(0.000)	(0.005)	(0.978)
Population density	-0.003**	-0.010*	-0.013**
	(0.027)	(0.062)	(0.026)
Income inequality index	0.045	-0.049	-0.004
	(0.248)	(0.583)	(0.965)
College graduate rate	-0.115*	0.052	-0.063
	(0.053)	(0.699)	(0.676)
Education spending per student	0.082	-0.060	0.022
	(0.515)	(0.829)	(0.943)
Poverty rate	-0.120	-0.152	-0.272
	(0.380)	(0.653)	(0.465)
Unemployment rate	0.140	0.648**	0.788***
	(0.213)	(0.014)	(0.004)
Uninsured rate	-0.020	-0.037	-0.058
	(0.655)	(0.741)	(0.662)
Per capita income	-3.540***	3.245**	-0.295
	(0.000)	(0.044)	(0.863)
ρ		0.23	
		(0.000)	
R^2		0.87	
Observations		784	

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

concept of consumers trying to maximize their utility. The consumption of opioids provides utility for a typical addict, although some economists have characterized an addict as an imperfect rational behavior that is struggling between ending addiction and adoring opioid consumption (Chaloupka et al. (1999)). Enactment of a Naloxone access law may affect current and future opioid consumption of addicted persons by reducing the cost of opioid consumption. By having access to Naloxone (sometimes inexpensive, but quick and effective medicine to reverse the consequences of overdosing), addicts may increase their propensity to consume opioids. Addicts thereby adjust their response to the law by continued opioid use with less fear and uncertainty of dealing with an overdose death (the moral hazard problem). The end result is that while administering Naloxone prevents an overdose death, the expanded ability to administer Naloxone does not reduce the death rate.

Our findings have policy implications for both federal and states governments. The provisions with negative coefficients (immunity from professional sanction for dispensers, third party authorization, and immunity from criminal liability for users) should definitely be included in any access law. However, it is problematic to interpret the results of Model 3 (model with Naloxone access law provisions) as some provisions should be included in laws (those with negative effects) while other provisions should be excluded from laws (those with positive effects). In practice, provisions with opposite effect signs often are included in most laws, examples include NAL 4 and 7 along with NAL 10 and 11. So interpretation of single provision effect without considering the effects of other provisions is not seen as particularly useful for policy implications.

A more preferred interpretation of Model 3 results is to aggregate across statistically significant effects for all provisions. When we assess the aggregate impacts for direct, indirect, and total effects, we find that in each case the net effect of Naloxone access laws is to increase opioid death rates both within and outside the states where these laws have been enacted. Looking across multiple provisions, these findings provide no statistical evidence that these laws reduce opioid death rates.

Our findings need to be viewed within a narrow context of Naloxone access laws as the sole policy response to the opioid crisis. As a policy response, Naloxone treats only the symptoms of addiction by preventing immediate death from an overdose, but does not prevent or treat addiction as the underlying cause of opioid related overdose deaths. Our results show that when access laws are evaluated in isolation of any other state level policy response to opioids, increasing access to Naloxone does not reduce, but leads to increased overdose death rates. Thus, the moral hazard perspective of this policy is the more accurate assessment of the outcome when access laws are the only policy. Immunity from civil liability for users and immunity from criminal liability for possession of Naloxone are provisions that show the change in behavior of the users and we see a positive effect of these laws on opioid overdose death rates.

Enactment of a Naloxone access law is a starting point in implementing and expanding access to save lives seems a necessary strategy, but not a sufficient response to the overdose problem. Apart from the law enactment, both federal and state governments should consider the next steps such as policy recommendation presented by Clark (2017) (e.g. team-based care model, more collaboration with pharmacists, minimize cost barriers to have access to Naloxone, expanding harm reduction treatment model). Both federal and state governments need to be involved in preventive policies more focused on regions not one specific state.

We recognize several limitations in our research. First, many states have only recently enacted Naloxone access laws. Since our data cover years 1999 to 2014, for those 10 states with newly enacted laws in 2014, we do not have post implementation data. Furthermore, 10 more states enacted laws in 2013, so that only one year of data is included in our dataset. Empirical results may change with more post implementation data for these 20 states. Second, county level analysis would be preferable to assess the spillover effects across states, but these data were not consistently available for overdose death rates.[37]

Further research should 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). In addition, research should examine 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.

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

References

(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.

(2017). Naloxone: Frequently Asked Questions. http://naloxoneinfo.org/sites/default/files/Frequently%20Asked%2 Naloxone_EN.pdf. Accessed on 01/16/2017.

(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.

Andrade, L. C. d. (2016). *Spillover effects of blacklisting policy in the Brazilian Amazon*. PhD thesis, Universidade de São Paulo.

Attila, V. (2000). Local academic knowledge spillovers and the concentration of economic activity.

Branas, C. C., Cheney, R. A., MacDonald, J. M., Tam, V. W., Jackson, T. D., and Ten Have, T. R. (2011). A difference-in-differences analysis of health, safety, and greening vacant urban space. *American journal of epidemiology*, 174(11):1296–1306.

Chagas, A. L., Azzoni, C. R., and Almeida, A. N. (2016). A spatial difference-in-differences analysis of the impact of sugarcane production on respiratory diseases. *Regional Science and Urban Economics*, 59:24–36.

Chaloupka, F. J., Tauras, J., and Grossman, M. (1999). Economic models of addiction and applications to cigarette smoking and other substance abuse. *Chicago, University of Illinois*, pages 1–27.

Chen, Z. and Haynes, K. E. (2015). Public surface transportation and regional output: A spatial panel approach. *Papers in Regional Science*, 94(4):727–751.

Clark, M. 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.

Coffin, P. O., Fuller, C., Vadnai, L., Blaney, S., Galea, S., and Vlahov, D. (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(2):288–290.

Coffin, P. O. and Sullivan, S. D. (2013). Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in russian cities. *Journal of Medical Economics*, 16(8):1051–1060.

Council, N. R. et al. (2004). *Indicators for waterborne pathogens*. National Academies Press.

Davis, C. (2015). Naloxone for community opioid overdose reversal. *Public Health Law Research. Retrieved June*, 25.

Davis, C. and Chang, S. (2013). Legal interventions to reduce overdose mortality: Naloxone access and overdose good samaritan laws. *The Network for Public Health Law*, 32(19):2.

Davis, C., Webb, D., and Burris, S. (2013). Changing law from barrier to facilitator of opioid overdose prevention. *The Journal of Law, Medicine & Ethics*, 41(s1):33–36.

Davis, C. S. and Carr, D. (2015). Legal changes to increase access to naloxone for opioid overdose reversal in the United States. *Drug and alcohol dependence*, 157:112–120.

Davis, C. S., Ruiz, S., Glynn, P., Picariello, G., and Walley, A. Y. (2014). Expanded access to naloxone among firefighters, police officers, and emergency medical technicians in Massachusetts. *American journal of public health*, 104(8):e7–e9.

Debarsy, N., Ertur, C., and LeSage, J. P. (2012). Interpreting dynamic space–time panel data models. *Statistical Methodology*, 9(1):158–171.

Delgado, M. S. and Florax, R. J. (2015). Difference-in-Differences Techniques for Spatial Data: Local Autocorrelation and Spatial Interaction. *Economics Letters*, 137:123–126.

Dimick, J. B. and Ryan, A. M. (2014). Methods for evaluating changes in health care policy: the difference-in-differences approach. *Jama*, 312(22):2401–2402.

Dubé, J., Legros, D., Thériault, M., and Des Rosiers, F. (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. P. (2014). *Spatial econometrics: from cross-sectional data to spatial panels*. Springer.

Enteen, L., Bauer, J., McLean, R., Wheeler, E., Huriaux, E., Kral, A. H., and Bamberger, J. D. (2010). Overdose prevention and naloxone prescription for opioid users in San Francisco. *Journal of Urban Health*, 87(6):931–941.

Galea, S., Ahern, J., Vlahov, D., Coffin, P. O., Fuller, C., Leon, A. C., and Tardiff, K. (2003). Income distribution and risk of fatal drug overdose in New York City neighborhoods. *Drug and alcohol dependence*, 70(2):139–148.

Gatti, U., Tremblay, R. E., and Schadee, H. M. (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(3-4):255–275.

Getis, A. (2007). Reflections on spatial autocorrelation. *Regional Science and Urban Economics*, 37(4):491–496.

Green, T. C., Dauria, E. F., Bratberg, J., Davis, C. S., and Walley, A. Y. (2015). Orienting patients to greater opioid safety: models of community pharmacy-based naloxone. *Harm reduction journal*, 12:25–25.

Green, T. C., Heimer, R., and Grau, L. E. (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(6):979–989.

Griffith, D. A. (2005). Effective geographic sample size in the presence of spatial autocorrelation. *Annals of the Association of American Geographers*, 95(4):740–760.

Hembree, C., Galea, S., Ahern, J., Tracy, M., Piper, T. M., Miller, J., Vlahov, D., and Tardiff, K. J. (2005). The urban built environment and overdose mortality in New York City neighborhoods. *Health & place*, 11(2):147–156.

Inocencio, T. J., Carroll, N. V., Read, E. J., and Holdford, D. A. (2013). The Economic Burden of Opioid-Related Poisoning in the United States. *Pain medicine*, 14(10):1534–1547.

Jaffe, A. B. (1989). Real effects of academic research. *The American economic review*, pages 957–970.

Jaffe, A. B., Trajtenberg, M., and Henderson, R. (1993). Geographic localization of knowledge spillovers as evidenced by patent citations. *the Quarterly journal of Economics*, 108(3):577–598.

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., and Galea, S. (2014). Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American journal of public health*, 104(2):e52–e59.

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

Lim, J. K., Bratberg, J. P., Davis, C. S., Green, T. C., and Walley, A. Y. (2016). Prescribe to Prevent: Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists. *Journal of addiction medicine*, 10(5):300.

Morris, S., Hunter, R. M., Ramsay, A. I., Boaden, R., McKevitt, C., Perry, C., Pursani, N., Rudd, A. G., Schwamm, L. H., Turner, S. J., et al. (2014). Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *Bmj*, 349:g4757.

Nandi, A., Galea, S., Ahern, J., Bucciarelli, A., Vlahov, D., and Tardiff, K. (2006). What explains the association between neighborhood-level income inequality and the risk of fatal overdose in New York City? *Social science & medicine*, 63(3):662–674.

Partridge, M. D., Boarnet, M., Brakman, S., and Ottaviano, G. (2012). Introduction: whither spatial econometrics? *Journal of Regional Science*, 52(2):167–171.

Rees, D. I., Sabia, J. J., Argys, L. M., Latshaw, J., and Dave, D. (2017). With a Little Help from My Friends: The Effects of Naloxone Access and Good Samaritan Laws on Opioid-Related Deaths. Technical report, National Bureau of Economic Research.

Richardson, R., Charters, T., King, N., and Harper, S. (2015). Trends in Educational Inequalities in Drug Poisoning Mortality: United States, 1994–2010. *American journal of public health*, 105(9):1859–1865.

Rowe, C., Santos, G.-M., Vittinghoff, E., Wheeler, E., Davidson, P., and Coffin, P. O. (2016). Neighborhood-Level and Spatial Characteristics Associated with Lay Naloxone Reversal Events and Opioid Overdose Deaths. *Journal of Urban Health*, 93(1):117–130.

Rudd, R. A., Aleshire, N., Zibbell, J. E., and Matthew Gladden, R. (2016). Increases in drug and opioid overdose deaths—United States, 2000–2014. *American Journal of Transplantation*, 16(4):1323–1327.

Ruhm, C. J. (2016). Drug poisoning deaths in the united states, 1999–2012: a statistical adjustment analysis. *Population health metrics*, 14(1):2.

Seal, K. H., Thawley, R., Gee, L., Bamberger, J., Kral, A. H., Ciccarone, D., Downing, M., and Edlin, B. R. (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(2):303–311.

Shah, N. G., Lathrop, S. L., Flores, J. E., and Landen, M. G. (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(1):19–26.

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

Sunak, Y. and Madlener, R. (2014). Local impacts of wind farms on property values: a spatial difference-in-differences analysis.

Tobler, W. R. (1970). A computer movie simulating urban growth in the Detroit region. *Economic geography*, 46(sup1):234–240.

Unick, G., Rosenblum, D., Mars, S., and Ciccarone, D. (2014). The relationship between US heroin market dynamics and heroin-related overdose, 1992–2008. *Addiction*, 109(11):1889–1898.

Visconti, A. J., Santos, G.-M., Lemos, N. P., Burke, C., and Coffin, P. O. (2015). Opioid overdose deaths in the city and county of San Francisco: prevalence, distribution, and disparities. *Journal of Urban Health*, 92(4):758–772.

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., and Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *Bmj*, 346:f174.

Wheeler, E., Davidson, P. J., Jones, T. S., and Irwin, K. S. (2012). Community-based opioid overdose prevention programs providing naloxone—United States, 2010. *MMWR. Morbidity and mortality weekly report*, 61(6):101.