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Abbreviations: AED = automated external defibrillators, CDC = centers for Disease Control and Prevention, NAL = naloxone accessibility law, OEND = overdose education and nasal naloxone distribution programs.

Keywords: drug policy, naloxone, overdose death, region

1. Introduction

Opioid use disorder and overdose deaths currently pose a grave threat to public health in the US. According to the Centers for Disease Control and Prevention (CDC), approximately 400,000 people died of opioid overdose between 1999 and 2017.^[1] Among the strategies implemented to resolve the issue, an increase in naloxone access by legal means through Naloxone Access Laws (NALs) has been proven to be effective in lowering the incidence of opioid overdose deaths.^[2]

Even with strong measures to address the issue, the number of opioid overdose deaths has been increasing.^[1] However, although the opioid death rates increased in most states, some states were stabilized or even decreased.^[1] According to a CDC report, there was a 71% increase of overdose death rates between 2013 and 2017 and an increase of 9% per year from 1999 to 2011. The CDC indicated, by citing previous studies, that opioid-involved death rate increases were more attributable to illicitly-manufactured fentanyl than to pharmaceutically-manufactured fentanyl.^[3–5] Fentanyl is 50 to 100 times more potent than morphine and has a rapid onset of action, leading to immediate respiratory depression and death. Thus, Reduction of opioid-related mortality rates requires cooperation among public health and legislative officials, in addition to improving naloxone accessibility. Public health authorities should develop more efficient surveillance systems for detecting and controlling drug overdose outbreaks, and legislative officials need to enact laws designed to reduce and control these outbreaks. One of the best options to halt explosive growth of opioid-involved overdose deaths is to allow laypersons to possess naloxone without prescription.

States with the highest observed age-adjusted drug overdose death rates require stronger measures to combat the burgeoning opioid epidemic. In particular, some states in the Northeast, such as Pennsylvania, New Hampshire, Maine, Massachusetts and Connecticut, fall into this category.^[6] However, previous studies have found regional imbalances between opioid overdose treatment capacity and need, especially in the Northeast states of Pennsylvania, New York and New Jersey.^[7] Naloxone, a competitive opioid antagonist, can rapidly reverse opioid overdose toxicity.^[8] The implementation of NALs increased accessibility of naloxone to the public in the US. Naloxone administration by bystanders improved the recovery rate from opioid overdose.^[9] However, state naloxone dispensing rates do not match opioid overdose death rates.^[10] While overdose education and naloxone distribution programs raised awareness and accessibility, there is possibility of a mismatch between naloxone possession and use by laypersons.^[11] The scope and extent of immunity provided by state legislations also differ; some allow laypersons to possess naloxone without prescription, but others allow only distribution.^[12] On April 5, 2018, the Office of the Surgeon General released a statement to urge further expansion of naloxone availability.^[13] The first step in furthering this expansion should be to amend law to permit layperson naloxone

possession, especially in regions where opioid overdose death reduction is most needed.

The objective of our study was to evaluate these regional differences and recent trends in drug overdose death rates in states with or without NALs.

2. Methods

2.1. Data source

Study design was a serial retrospective cross-sectional data analysis.^[14] We obtained data from the National Vital Statistics Systems presenting provisional counts for drug overdose deaths occurring in 50 states and the District of Columbia from 2013 to 2017. The counts represented the number of reported deaths due to drug overdose occurring in the 12-month periods ending in the months indicated. Information on state NALs was obtained from the Prescription Drug Abuse Policy Surveillance Systems as well as academic and legal sources. Additionally, we referred to the US Census Bureau Region and Census Division for regional classifications in reference to states with and without NALs. Approval by an Institutional Review Board was not necessary because all data were secondary, de-identified, and publicly available and patients' consent was not involved.

2.2. Main measurement and variables of interest

Drug overdose deaths were identified in the National Vital Statistics System multiple cause-of-death mortality files from data contained on death certificates.^[14] The National Vital Statistics System is an inter-governmental system to share data regarding the vital statistics of the US population.^[14] The cause of death is coded based on the International Classification of Disease-10 codes X40-44 (unintentional), X60-64 (suicide), X85 (homicide), or Y10-14 (undetermined intent). Among deaths with drug overdose as the underlying cause, the type of drug or drug category is demonstrated by the following International Classification of Disease, 10th revision, Clinical Modification multiple cause-of-death codes: T40.0, narcotics and psychodysleptics; T40.1, heroin; T40.2, other opioids such as natural and semisynthetic opioids; T40.3, methadone; T40.4, other synthetic narcotics, excluding methadone; T40.5, cocaine; and T43.6, psychostimulants with abuse potential. Some causes of deaths involved more than 1 type of drug, and these were included in rates for each drug category; thus, causes of death in some cases were not mutually exclusive. For example, a death involving both a synthetic opioid other than methadone and heroin would be included in both the synthetic opioid other than methadone and heroin death rates. All annual drug overdose death rates were presented as number of deaths per 100,000 persons. We examined the outcomes of interest, state-level annual drug overdose death by region, as defined by the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. We focused on the Western and Northeastern states, which are unlikely to have neighboring effects on each other, to discern which regions need stronger legislative measures.

Table 1**Age-adjusted drug overdose death rates according to state by layperson distribution.****Northeast (n = 9)**

Layperson distribution				No layperson distribution			
State	Average change		13.57 Difference	State	Average change		15.15 Difference
	2013	2017			2013	2017	
Maine	9.9	29.9	20	Connecticut	12.3	27.7	15.4
New Hampshire	11.8	34	22.2	Massachusetts	13.3	28.2	14.9
New Jersey	7.6	22	14.4				
New York	8.3	16.1	7.8				
Pennsylvania	7.8	21.2	13.4				
Rhode Island	18.1	26.9	8.8				
Vermont	11.6	20	8.4				

West (n = 13)

Layperson distribution				No layperson distribution			
State	Average change		0.34 Difference	State	Average change		6.17 Difference
	2013	2017			2013	2017	
Alaska	9.2	13.9	4.7	Arizona	8.2	13.5	5.3
California	4.9	5.3	0.4	Idaho	5.7	18.8	13.1
Colorado	8	10	2	Wyoming	8.6	8.7	0.1
Hawaii	4.7	3.4	-1.3				
Montana	7.2	3.6	-3.6				
New Mexico	16	16.7	0.7				
Nevada	13.7	13.3	-0.4				
Oregon	7.5	8.1	0.6				
Utah	15.9	15.5	-0.4				
Washington	8.9	9.6	0.7				

*State abbreviations are in alphabetical order.

*All death rates are per 100,000 populations.

2.3. Statistical analysis

We adopted the statistical results from a previous study.^[1] The study performed statistical analysis of state-level average annual percentage changes in age-adjusted drug overdose death rates from 2013 to 2017.^[1] Annual percentage changes with statistically significant trends were analyzed using z-tests when the number of deaths was ≥ 100 and non-overlapping confidence intervals based on a gamma distribution when the number was < 100 . Scholl L et al described the statistical analysis in more detail.^[1]

3. Results

Seven states in the Northeast region and 10 states in the Western region allowed layperson distribution of naloxone. Layperson possession of naloxone was allowed in 3 states each in the Northeast and the Western regions.

Table 1 presents age-adjusted drug overdose death rates according to state by layperson distribution availability. In the Northeast region, seven states that allowed layperson distribution of naloxone showed an increase in age-adjusted drug overdose death rate between 2013 and 2017. The average increase in the death rate was 13.57 per 100,000 persons. Two states in the Northeast region that did not allow layperson distribution of naloxone showed an average increase in death rate of 15.12 per 100,000 persons, which was slightly higher than that of the states with naloxone distribution. The Western states generally showed smaller changes in age-adjusted drug overdose death rates than those of the Northeast. The 3 Western states that allowed naloxone distribution showed an average increase in

death rate of 0.34 per 100,000 persons; this was significantly lower than that of the Western states that did not allow naloxone distribution (6.17 per 100,000 persons).

Table 2 shows age-adjusted drug overdose death rates according to state by layperson possession. Three Western states that allowed possession of naloxone showed a -0.33 per 100,000 persons decrease in average overdose death rate. This is the only group that showed a decrease in drug overdose death rate from 2013 to 2017. The other 10 Western states that did not allow naloxone possession showed an increase in death rates at an average of 2.53 per 100,000 persons. In the Northeastern region, 3 states that allowed layperson possession of naloxone showed significantly smaller increases in death rates, an average of 10.7 per 100,000 persons, compared to the 15.53 per 100,000 persons average of 6 states that did not allow naloxone possession.

4. Discussion

We found regional variation of drug overdose death rates that appeared to be associated with scope and extent of NAL provisions. In the Western region, drug overdose death rates decreased in the states that allowed layperson naloxone possession. Sharp increases in drug overdose death rates in the Northeastern region were partially alleviated in the states allowing layperson naloxone possession.

Despite efforts to solve the opioid epidemic issue, numbers of hospitalizations and emergency department visits and net opioid overdose death rates are on the rise.^[4,15,16] However, the pace at which the overdose death rates has grown differs by

Table 2**Age-adjusted drug overdose death rates according to state by layperson possession.**

Northeast (n = 9)							
Layperson possession				No layperson possession			
State	Average change		10.7 Difference	State	Average change		15.53 Difference
	2013	2017			2013	2017	
Massachusetts	13.3	28.2	14.9	Connecticut	12.3	27.7	15.4
Rhode Island	18.1	26.9	8.8	Maine	9.9	29.9	20
Vermont	11.6	20	8.4	New Hampshire	11.8	34	22.2
				New Jersey	7.6	22	14.4
				New York	8.3	16.1	7.8
				Pennsylvania	7.8	21.2	13.4

West (n = 13)							
Layperson possession				No layperson possession			
State	Average change		-0.33 Difference	State	Average change		2.53 Difference
	2013	2017			2013	2017	
Hawaii	4.7	3.4	-1.3	Alaska	9.2	13.9	4.7
New Mexico	16	16.7	0.7	Arizona	8.2	13.5	5.3
Nevada	13.7	13.3	-0.4	California	4.9	5.3	0.4
				Colorado	8	10	2
				Idaho	5.7	18.8	13.1
				Montana	7.2	3.6	-3.6
				Oregon	7.5	8.1	0.6
				Utah	15.9	15.5	-0.4
				Washington	8.9	9.6	0.7
				Wyoming	8.6	8.7	0.1

*State abbreviations are in alphabetical order.

*All death rates are per 100,000 populations.

states. This difference in pace can partially be explained by the differences in extent to which lay people have access to naloxone. States that allowed layperson possession without prescription demonstrated slower increases in opioid overdose death rates compared to those that did not.^[17] Increasing possession of naloxone by lay responders is more directly related to reducing overdose death than increasing distribution. Although awareness and accessibility of naloxone rose, naloxone possession may be different from its actual use.^[11] Some speculate that individuals may be reluctant to carry naloxone in fear of harassment from law enforcement due to the association between naloxone and opioid use. Therefore, reducing the stigma attached to possession by legal means will be pivotal to overdose prevention. Efforts should be made to make naloxone more available not only by means of treatment and prescription but also by involving laypersons.

Previous findings suggested that witnessing an overdose or knowing someone affected by overdose were potential motivators for first-time naloxone access among lay responders.^[18] However, the general public, including opioid users, may not be aware of naloxone access. Programs like overdose education and nasal naloxone distribution programs (OEND) have attempted to educate opioid users and bystanders to prevent, recognize, and respond to overdose with use of naloxone. According to the interrupted time series analysis performed by Walley et al., communities where OEND was implemented displayed reduced opioid overdose death rates compared to those with no OEND.^[19] There needs to be a nationwide effort led by policy-makers to expand naloxone education programs like OEND targeting not only opioid users and their families but also general public.^[20]

Naloxone has become more available with implementation of NALs. However, naloxone's distribution system needs to be optimized. Automated external defibrillators (AEDs) have become widely available and encouraged for public use. Thus, naloxone kits can be added to the AED cabinets.^[21] However, locating AEDs in public place can be difficult in certain locations, resulting in greater delay before implementation.^[22] If AEDs were used as landmarks for naloxone kits, the same issue will be present for administration in an emergent overdose scenario. To counteract this, a national registry of naloxone kit locations should be implemented as well. Smartphone technology with a global positioning system directing bystanders to the location of the emergency, which has been shown to increase the rates of cardiopulmonary resuscitation by bystanders, could also be used to help bystanders locate the nearest naloxone kit.^[23] Applications, such as NaloxoFind, have been used to identify and locate naloxone within a 2 mile radius and allows communication with those carrying naloxone.^[24] Further promotion of such technology will increase use of available naloxone in public.

These results indicate that legislation needs to be revised to maximize naloxone availability by permitting laypersons to possess naloxone without prescription, especially in states where the problems are rising. With statewide adoption of legislation designed to improve layperson naloxone access, policy-makers need to assess the effectiveness in delivery and impact of these policies. The opioid epidemic is a nationwide catastrophe. It can affect our lives directly or indirectly. To alleviate the opioid crisis, multidisciplinary approaches by personnel from a variety of fields such as government, community, and academia are required. Health professionals, especially opioid prescribers, are also at the forefront of the fight against the opioid epidemic. These

professionals should be well-versed in naloxone prescription practices and education on its proper use. In addition to legislation of NALs, fund-raising, community education and training for stakeholders, providing treatment programs and facilities, and policy-making are necessary. A community coalition model such as Project Nazarus provides a good example for us to improve opioid overdose outcomes.^[2,5] Project Nazarus involves community activation and coalition building, monitoring and surveillance system, overdose prevention, rescue medication for reversing drug overdoses, and assessment of project components. In Project Nazarus, stakeholders from various sectors such as healthcare, school, police, and substance abuse facilities, have participated in this model and committed to engage the support from relevant parts in the community. Through a community forum, they share information, raise awareness of the community's problems, and bring the attention of other people. In addition, they establish a working coalition and a community plan and make policies to resolve problems. Providing naloxone to the public and teaching them its proper use will improve responsibility and power to reduce the opioid epidemic. In order to develop sustainable policies, cost-effectiveness should be considered. Increased naloxone distribution and possession may increase medical expenditures and the public health budget. Because opioid use is high contagious and the consequences can be fatal, health authorities need to pay the cost even if NALs are not cost-effective. In addition, the ethical and psychological aspects should be considered. The social effort to reduce the stigma regarding opioid use and naloxone possession and emotional supports for drug users to return to their communities are required. Understanding the biopsychosocial nature of substance disorder and evidence-based interventions to resolve this growing problem are necessary.

We acknowledge several limitations. First, we did not use primary death certificate data but used the secondary data. This limitation can result in some biases. Second, low sensitivity and high specificity in weighted estimates occurred when identifying persons who use illicit drugs from administrative claim data.^[26] Third, other factors involved in reducing opioid overdose death rates have not been considered and, therefore, not controlled. This is particularly true in terms of assessing the actual impact of legalization of layperson naloxone possession on death rates. Beyond NALs, other conditions may have influenced clinical outcomes. In addition, only northeast and west regions were investigated in this study in order to minimize neighboring effects. Thus, further studies should be warranted to assess that increased naloxone accessibility decreases opioid overdose deaths in other regions after controlling for confounding factors. Fourth, whether or not more laypersons possessed and used naloxone for rescue after establishment of NALs is difficult to surmise, although there is some indirect evidence. Nationwide naloxone dispensing increased nearly 8-fold from the 4th quarter of 2015 to the 2nd quarter of 2017.^[10] The Surgeon General emphasized the importance of awareness and distribution of naloxone to the public. This study demonstrated that layperson possession might be associated with reduced growth of the opioid overdose death rate. In addition, because of the possibility of under-reporting of overdose deaths or lag times from coroner reports, the data may underestimate opioid overdose deaths. Fifth, we used the state-level data that could distort the results than the county- or city-level data. Despite these potential limitations, the strength of this study is provision of several new insights into the opioid crisis from a public health perspective. This study demonstrated the

association between NAL provisions (possession vs distribution) and their effects on opioid overdose death according to geographic location (Northeast vs West).

In conclusion, we found that the greater was the access to naloxone, the lower were the drug overdose death rates. Age-adjusted drug overdose death rates in states that allowed layperson distribution were lower than those in states that did not. These death rates showed a similar pattern according to layperson possession; the death rates were lower in states that allowed layperson possession than in states that did not. These findings support the assertion that improved naloxone accessibility will ameliorate drug overdose death.

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