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The effect of opioid overdose education and Naloxone distribution programs on opioid-related mortality

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The Effect of Opioid Overdose Education and Naloxone Distribution Programs on Opioid-Related Mortality

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Abstract:

Objective: To determine the effectiveness of opioid overdose education and naloxone distribution (OEND) program implementation in reducing opioid-related overdose mortality. **Methods:** A PubMed search was conducted using the terms “opioid overdose prevention community naloxone,” yielding 80 records, 36 of which were screened. The remaining 44 articles were reviewed for eligibility, resulting in three articles chosen for the study. **Results:** An interrupted time-series analysis by Walley et al., and two retrospective cohort studies by Albert et al. and Rowe et al. were analyzed. **Conclusion:** Studies by Walley et al. and Albert et al. demonstrated a positive association between OEND program implementation and a decrease in opioid-related mortality rates. Due to data variability, OEND program effectiveness could not be extrapolated with Rowe et al.; however, the study provided insight into targeting demographic characteristics for OEND program implementation. To address the national opioid epidemic, strategic, community-level efforts that leverage available resources should be used to establish OEND programs.

Key: OEND = Opioid overdose education and naloxone distribution

Introduction:

Nonmedical use and misuse of opioids is a public health emergency in the United States. Since 1999, the rate of opioid overdose has quadrupled.[1] In 2013, approximately 2 million Americans reported nonmedical and misuse of opioids, which attributed to an estimated economic burden over $78 billion in expenses related to health care, criminal justice, and lost productivity.[2,3] In 2015, opioids accounted of over 33,000 deaths across all 50 states and the District of Columbia, with prescription opioids accounting for over 22,000 deaths.[4,5] In 2017, the Centers for Disease Control and Prevention (CDC) estimate that over 90 Americans die each day due to opioid overdoses. [6]

Opioids are chemicals that bind to opioid receptors on nerve cells in the body and brain, which helps to reduce the intensity and sensation of pain. Acute and chronic pain can be treated with opioids; however, a prescription is required from a licensed clinician. Prescription opioids can be categorized as natural like morphine or codeine, semisynthetic like oxycodone or hydrocodone, or synthetic like tramadol or fentanyl. Illicit opioids, or those which are non-medical and prohibited by law, are found in the United States with heroin being the most used.[7] Both prescription and illicit opioids can be sources of nonmedical use and misuse, which can lead to overdose and death often secondary to respiratory depression.[3,8] Respiratory depression from opioid use can be reversed with administration of the medication naloxone, an opioid receptor antagonist.[8,9]

To address nonmedical use and misuse of opioids the President of the United States declared that the opioid crisis was a public health emergency on October 26, 2017. [3] This declaration was preceded by numerous federal, state, and local level efforts to address the growing epidemic. Specifically, in April 2017 the U.S. Department of Health and Human Services (HHS) announced a 5-point strategy for fighting the opioid crisis.[6] This comprehensive strategy outlined the following to address nonmedical use and misuse of opioids: better data on

the epidemic; better pain management; better prevention, treatment & recovery services; better targeting of overdose reversing medications; and better research into pain and addiction.[10] Further, in Fiscal Year 2017 HHS provided just under $1 billion in opioid-specific funding to state and local governments and civil society groups to support strategies to combat the public health emergency.[11]

Current strategies to address nonmedical use and misuse of opioids include prescription drug monitoring programs, development of guidelines for safe opioid prescribing, development of treatment and rehabilitation programs for opioid users, implementation of opioid education programs to reduce overdose, nonmedical use and misuse, and targeting of overdose reversing medications like naloxone.[11,12] These strategies lack quantitative studies supporting reduction of overdose rates and deaths secondary to nonmedical use and misuse of opioids; this lack of data is acknowledged by the HHS 5-point strategy for fighting the opioid crisis which aims to address this deficit. [10,12]

The data gap supporting strategies to reduce nonmedical use and misuse of opioids does not correlate to a lack of implementation these programs. Some of these strategies have been implemented for many years by state and local governments and civil society groups. [12] Specifically, opioid overdose education and naloxone distribution (OEND) programs have been training citizens across the United States since at least 1996. In 2010, the CDC estimated that these OEND programs had successfully trained at least 53,000 lay rescuers for those that may overdose while using opioids, which was attributed with over 10,000 opioid overdose reversals with naloxone.[12] However, few studies attempt to quantify OEND program effectiveness at reducing opioid-related mortality.[13] Insufficient data could limit government funding for implementation OEND program in the future.

The current study looks to identify and analyze existing quantitative research of OEND program implementation to examine the effectiveness of OEND programs at reducing mortality of those that overdose on opioids in the United States. Further, this study aims to make recommendations for effective OEND implementation.

Clinical Question:

Among opioid users, does implementation of OEND programs as compared to no OEND program implementation decrease unintentional mortality rates secondary to opioid overdose (Table 1)?

Table 1: PICO criteria for clinical question

Population	Opioid users
Intervention	OEND program implementation
Comparison	No OEND program implementation
Outcome	Decreased unintentional mortality rates secondary to opioid overdose

Methods:

An initial search on PubMed was conducted in September 2018 using the terms “opioid overdose prevention community naloxone.” This query yielded 80 articles, without duplicates (Figure 1). The search was then limited to publications within the last seven years, texts with full availability, and human subjects only, resulting in 44 articles for manual review (Figure 1).

Articles were excluded if they only addressed the educational component of OEND programs (n=7), surveyed solely perspectives on the topic (n=4), or were non-original studies (n=3) (Figure 1). Studies were also eliminated if naloxone was administered in a health-care setting or by law enforcement officers (n=5), lacked mortality rates after OEND program intervention (n=6), or did not address the clinical question (n=16) (Figure 1). Thus, three articles remained: a time series analysis, retrospective study, and a spatial characteristics study (Figure 1).

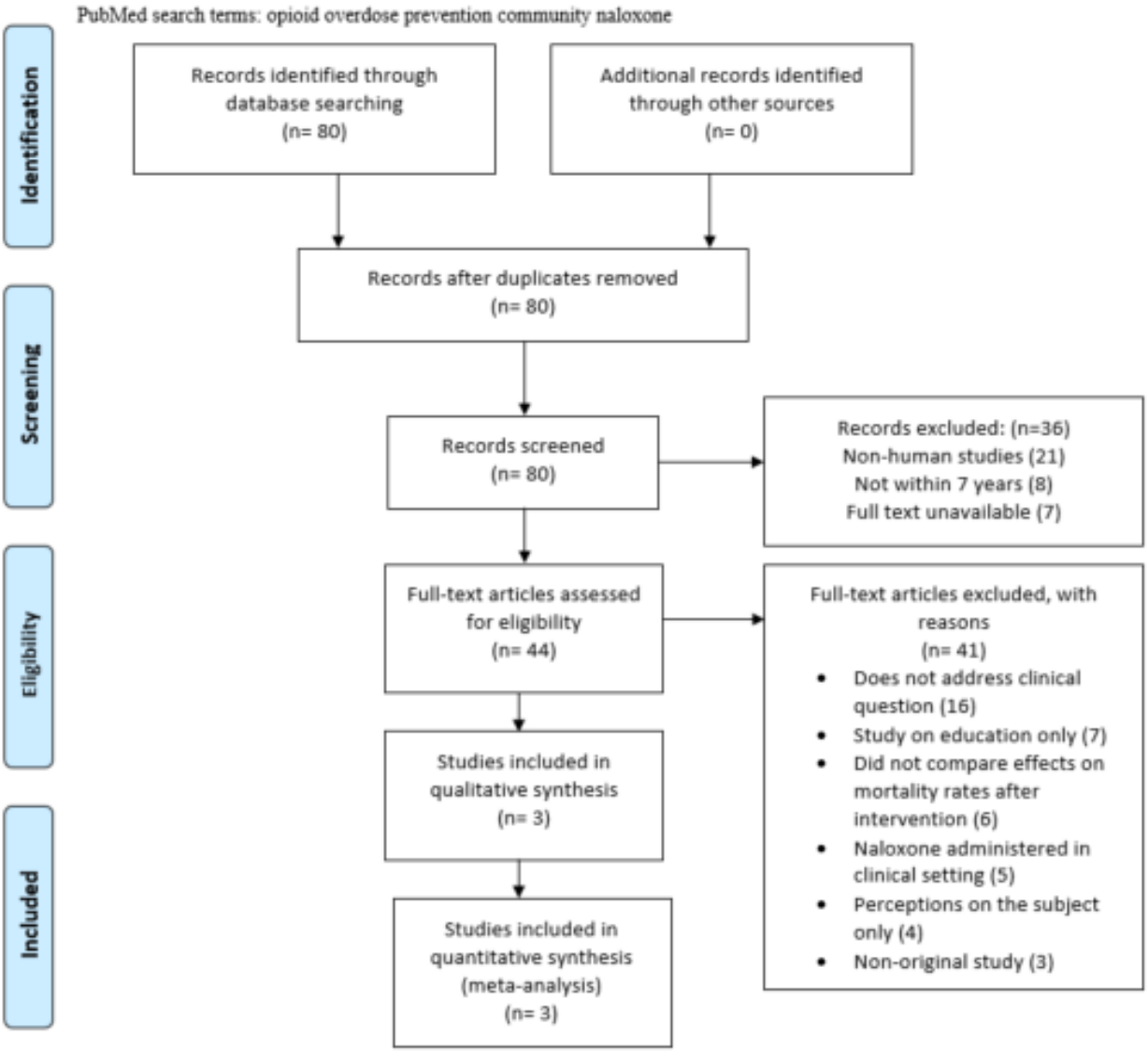

Figure 1. The PRISMA Flow Diagram outlines the selection process of the three articles analyzed for the current study. [14]

Results:

Study #1: *Opioid Overdose Rates and Implementation of Overdose Education and Nasal Naloxone Distribution in Massachusetts: Interrupted Time Series Analysis.*[12]

Objective:

To evaluate the effects of OEND program implementation on number of opioid related deaths in communities in Massachusetts with high rates of opioid overdoses.

Study Design:

The study conducted an interrupted time series analysis, between 2002-2006, that compared annual opioid related deaths in 19 Massachusetts communities with high and low rates of OEND program implementation, to communities without implementation. The communities are geographically distinct cities and towns that make up a third of Massachusetts's population and contribute to half of the opioid related overdoses.

The Massachusetts Department of Public Health provided the training to opioid users who were at risk for overdose, as well as family, friends, and social services staff. OEND program locations included needle exchange programs, HIV education centers, drug abuse treatment programs, primary care offices, emergency departments, and community support group meetings.

Information was collected from questionnaires at initial enrollment and when a refill for a naloxone rescue kit was requested. Enrollment questions included residing zip code, drug use, and history of overdose. Questions at the time of refill included the number of rescue attempts made by the bystander and whether naloxone was successful, as indicated by improvement of respiratory depression and unresponsiveness. In the 19 selected communities, zip codes were used to categorize enrollment rates as high OEND program implementation (>100 per 100,000 population), low implementation (1-100 per 100,000 population), and no implementation. Death certificates on opioid overdoses, which are required to be reported, were collected from the Massachusetts Registry of Vital Records and Statistics. Only unintentional or undetermined intentional opioid related deaths in the death field were included in the study.

Data adjustments were made for differences in overdose risk based on demographics and utilization of drug treatment programs. The Prescription Monitoring Program was also referenced to adjust for "doctor shoppers," defined as individuals who obtained opioid prescriptions from more than three prescribers and filled prescriptions at more than three pharmacies in a 12-month period.

The Poisson regression model was applied to analyze the rate of annual opioid related overdose deaths in relation to community-year strata with no, low, and high OEND program implementation, using significance level of 0.05. After regression diagnostics, first order autoregressive covariance structure was selected to account for repeated measures.

Inclusion Criteria:

The study included communities in Massachusetts with five or more opioid related deaths annually between years 2004 to 2006. Individuals included in the research were required to reside in one of the selected communities, and enroll in an OEND program.

Study Results:

During 2002-2005, OEND program was not implemented in the 19 Massachusetts communities. In 2006, seven of the selected communities had some implementation, which increased to 14 the following year. By 2008-2009, all 19 communities of interest included OEND program implementation.

Among these 19 communities, OEND programs trained 2,912 potential bystanders between September 2006 and December 2009. During this time, 327 naloxone rescue attempts were reported (Table 2). Of 153 rescue attempts, Naloxone was 98% successful (150/153), while the individuals of the three unsuccessful naloxone rescue attempts (3/153) survived by emergency medical services. The remaining rescue attempts were not calculated into the percentage due to missing information.

As the absolute number of OEND program enrollments increased, opioid related death rates demonstrated a decline. After adjusting for possible confounding variables, the enrollment to death rate ratios were significantly reduced in a dose related trend in both the community-year strata with low enrollment 1-100 per 100,000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and high enrollment >100 per 100,000 population (0.54, 0.39 to 0.76), as compared to communities without enrollment (Table 3).

Table 2: Overdose rescue attempts using naloxone, reported by OEND program trained bystanders from 2006 to 2009 in 19 Massachusetts communities.

Variables	**Rescue attempts** (Total number=327*)
Number of doses used:	
1	48% (149/312)
2	48% (150/312)
≥3	4% (13/312)
Naloxone successful	98% (150/153)
Emergency services activated	33% (106/326)

*Denominators less than 327 are due to missing information.

Table 3: OEND program enrollment and opioid related overdose death rates in 19 Massachusetts communities, from 2002 to 2009.

OEND* enrollments per 100,000 population	Unadjusted rate ratio	Adjusted rate ratio^ (95% confidence interval)	*p* value
No enrollment	Reference	Reference	
Low enrollment 1-100	0.93	0.73 (0.57 to 0.91)	<0.01
High enrollment >100	0.82	0.54 (0.39 to 0.76)	<0.01

*OEND = Opioid Overdose Education and Naloxone Distribution
^Adjusted for population under the age of 18, race, below poverty level, utilization of withdrawal or maintenance treatment program, doctor shoppers, and year.

Study Critique:

The study used a large sample size and the authors extensively addressed and adjusted for potential confounding variables among opioid users, increasing the reliability of the study. Further, the study performed two grades of intervention, both high and low OEND program implementation. These tiers allowed for the evaluation of dose-related effects, which may be helpful for future communities looking to establish OEND programs.

Another strength of the study was the comparison of death rates among communities with and without OEND program implementation during concurrent years. This side by side analysis decreased potential differences due to extraneous variables of the naturally occurring environment as well as trends of the time period. However, one year after OEND program implementation, opioid related death rates in communities without OEND program implementation were no longer included. It would have been beneficial to compare each community-year strata until the conclusion of the study in 2009.

Approximately half of the reported rescue attempts were included in calculating the success rate of the naloxone intervention. The remaining attempts were discarded due to missing information without further specification or suggestion for improving follow up. The two figures provided in the article displayed unadjusted rates of opioid related overdose deaths; it would be beneficial to incorporate graphs using the adjusted data as this was statistically significant. Lastly, the raw data used in the analysis was not included anywhere in the study or supplemental materials; providing this information would have increased the validity of the results.

Study #2: *Neighborhood-Level and Spatial Characteristics Associated with Lay Naloxone Reversal Events and Opioid Overdose Deaths*.[13]

Objective:

To quantitatively examine census tract demographics and spatial data associated with implementing an OEND program to determine effectiveness and identify possible patterns coinciding with opioid abuse and OEND program location.

Study Design:

The study analyzed data regarding opioid overdose deaths and naloxone reversal events occurring within the City and County of San Francisco, CA, from January 1, 2010, and December 31, 2012. The California Electronic Death Reporting System, a statewide repository of all county-level death certificates, was used to export data for opioid overdose deaths. The data for naloxone reversal events were obtained from an OEND program in San Francisco, known as the Drug Overdose Prevention Education Project, which obtains information regarding naloxone administration from program participants when they return to a project site to obtain a new naloxone kit. The opioid overdose deaths and naloxone reversal events were geocoded into data points. These data points were geospatially compared to OEND program implementation sites, using ESRI ArcGIS, to calculate distance in meters from the data points to the nearest OEND program location. Further, these data points were analyzed with census tract data from the 2009 - 2013 American Community Survey 5-Year Estimates to determine if associations existed between population characteristics and naloxone reversal events or opioid overdose deaths. The census tract data contained information regarding population characteristics like median income, Gini coefficient, number of drug arrests, and population density.

The Wilcoxon rank-sum tests were utilized to compare these census tract population characteristics to naloxone reversal events and overdose deaths between the 44 census tracts with or adjacent to an OEND program site and the remaining 151 census tracts in the City and County of San Francisco, CA. The Kruskal-Wallis tests were employed to assess for associations between the census tract population characteristics and naloxone reversal events and overdose deaths, without adjusting for OEND program location within or near census tracts.

The researchers further assessed if variation in distance existed between the nearest OEND program location and the 24 census tracts with heroin-related overdose deaths and the 95 census tracts that only had opioid overdose deaths not related to heroin using a Wilcoxon rank-sum statistical test.

Negative binomial regression models were used to determine if independent association existed between the distance to the nearest OEND program site and both the number of naloxone reversal events and the number of opioid overdose deaths. Census tract population demographics and population size served as the units of measure for this multivariable analysis.

Inclusion Criteria:

The study included data of naloxone reversal events and opioid overdose deaths events from January 1, 2010, to December 31, 2012, if they occurred within the City and County of San Francisco, California. Only naloxone reversal events obtained from the OEND program sites were included. Further, only opioid overdose deaths of residents of the City and County of San

Francisco, California, who were 18 years old and older were included. Of the 17 OEND program sites only 11 were included as they distributed naloxone for more than half of the 36 months of the study period.

Study Results:

During the study period, 316 naloxone reversals and 342 opioid overdose deaths occurred that were included in the data analysis. The 44 census tracts with or adjacent to an OEND program site were found to have a significantly higher Gini coefficient, population density, drug arrests, naloxone reversal events and overdose deaths (Table 4).

In relation to distance to the OEND program site, both naloxone reversal events and opioid overdose deaths declined with increasing distance (Table 5). However, naloxone reversal events and opioid overdose deaths increased with increasing population density and number of drug arrests (Table 5). Further, a significant association was found between overdose deaths and decreasing median income and increasing Gini coefficient; this pattern was not observable for naloxone reversal events (Table 5).

The 24 census tracts with heroin-related overdose deaths were found to be significantly closer to OEND program sites when compared to the 95 census tracts that only had opioid overdose deaths not related to heroin (Table 6).

With the multivariable negative binomial regression models, naloxone reversals were independently and significantly associated with increasing proximity to OEND program sites and with more census tract drug arrests (Table 7). When applying the multivariable negative binomial regression model to opioid overdose deaths, there was a significant association with increasing number of drug arrests, increasing population size, and decreasing median income; however, there was no statistically significant association between overdose deaths and distance to nearest OEND program site (Table 8).

Table 4: The average values of census tract characteristics and comparison between census tracts without and not adjacent to an OEND site and census tracts with or adjacent to OEND sites in San Francisco, California, from 2010 to 2012, using Wilcoxon rank-sum statistical tests.

Census tract characteristics	Census tract with or adjacent to a census tract with an OEND* site	Census tract without or not adjacent to a census tract with an OEND* site	*p* value
***N* %**	151 (77%)	44 (23%)	
Gini coefficient`	0.459	0.478	0.038
Drug arrests	32	321	<0.001
Population density	9.6	17.1	<0.001
Overdose deaths^	1.0	4.5	<0.001
Reversal events^	0.2	6.5	<0.001

*OEND = Opioid Overdose Education and Naloxone Distribution

`Gini coefficient = Measure of income inequality

^Average per San Francisco census tract from January 1, 2010 and December 31, 2012.

Table 5. The comparison of averaged opioid overdose deaths and reversal events across averaged census tract characteristics, which were then divided into quartiles, from San Francisco, California, from 2010 to 2012. Statistical analysis was performed using the Kruskal-Wallis variance tests.

			Quartiles of census tract characteristics (mean values)				
Census Tract Characteristics		All census tracts (mean values)	First quartile	Second quartile	Third quartile	Fourth quartile	*p* value
Distance to OEND* site (m)		2478	532	1493	2912	5125	
	Overdose deaths	1.8	4.2	0.9	0.9	0.9	<0.001
	Naloxone reversals	1.6	5.7	0.3	0.03	0.01	<0.001
Median income		$79,621	$36,756	$68,813	$88,565	$123,476	
	Overdose deaths	1.8	4.3	1.1	1	0.7	<0.001
	Naloxone reversals	1.6	4.8	0.8	0.6	0.5	0.193
Gini coefficient^		0.463	0.386	0.436	0.481	0.548	
	Overdose deaths	1.8	0.8	1.7	1.5	3	0.024
	Naloxone reversals	1.6	0.3	1.1	1.6	3.5	0.165
Drug arrests		97	5	16	34	338	
	Overdose deaths	1.8	0.6	0.7	1.1	4.7	<0.001
	Naloxone reversals	1.6	0.1	0.3	0.4	5.7	<0.001
Population Density		11.4	4	8.3	11.1	22.4	
	Overdose deaths	1.8	0.9	1.1	1.8	3.3	0.011
	Naloxone reversals	1.6	0.7	0.3	2.4	3.1	<0.001

*OEND = Opioid Overdose Education and Naloxone Distribution
^Gini coefficient = Measure of income inequality

Table 6: The comparison of distance to nearest OEND program site between census tracts with heroin-related overdose death and those without heroin-related opioid overdose deaths in San Francisco, California, from 2010 to 2012, using Wilcoxon rank-sum statistical test.

	Census tracts with heroin-related overdose death	**Census tracts with non-heroin-related overdose death**	***p* value**
***N* (%)* Mean distance to nearest OEND^ site**	24 (20%) 1251	95 (80%) 2534	<0.001

*Percentage out of 119 census tracts with at least one opioid overdose death
^OEND = Opioid Overdose Education and Naloxone Distribution

Table 7: The multivariable negative binomial regression models analyzing associations between census tract characteristics and naloxone reversals in San Francisco, California, from 2010 to 2012.

	IRR*	(95% CI)	*p* value
Distance to OEND^ site (up to 4,000 m)	0.51	(0.39-0.67)	<0.001
Drug arrests (Log10 units)	1.50	(1.34-1.68)	<0.001

*IRR = Incident rate ratio

^OEND = Opioid Overdose Education and Naloxone Distribution

Table 8: Multivariable negative binomial regression models analyzing associations between census tract characteristics and opioid overdose deaths in San Francisco, California, from 2010 to 2012.

	IRR*	(95% CI)	*p* value
Distance to OEND^ site (up to 4,000 m)	0.00	(0.76-1.02)	0.093
Median income ($10,000 units)	0.93	(0.87-0.99)	0.021
Drug arrests (Log10 units)	1.50	(1.34-1.68)	<0.001
Population size (1000 units)	1.10	(1.02-1.19)	0.015

*IRR = Incident rate ratio

^OEND = Opioid Overdose Education and Naloxone Distribution

Study Critique:

The strengths of this study include a retrospective cohort, with a large sample size obtained from an urban population with widespread targeted implementation of an OEND program, and descriptive statistics including bivariate and multivariable analysis using pertinent census tract demographics. These strengths provide statistically significant quantitative data regarding associations between OEND program implementation and census tract community demographics. The findings of this study can provide meaningful suggestions for improving OEND programs implementation in across the United States of America.

The study is hampered by an underdeveloped discussion. The authors conclude an independent association between distance to nearest OEND program sites and naloxone reversals, with more naloxone reversals occurring closer in proximity to OEND program sites.

However, only heroin-related opioid overdose deaths increased in proximity to OEND program sites not overall opioid overdose deaths. While the authors identify that the OEND program sites were strategically placed in areas of historically high heroin-related opioid overdose deaths, they do not attempt to associate OEND program sites to fostering heroin-related opioid use, which might be concluded by the higher naloxone reversals and heroin-related deaths that occur closer to OEND program sites. Historical data regarding opioid overdose deaths from census tracts in the study would be beneficial for providing clarity to potential associations between OEND program site locations and increasing heroin-related opioid use.

Study #3: *Project Lazarus: Community-Based Overdose Prevention in Rural North Carolina*.[15]

Objective:

To study the effects of community-based opioid overdose prevention interventions on overdose mortality rates in Wilkes County, North Carolina.

Study Design:

The retrospective cohort study evaluated multi-modal opioid overdose prevention strategies implemented between 2005 to 2010, on death rates from poisonings in Wilkes County, North Carolina. The interventions were created as a response to the overdose death rates in Wilkes County reaching among the highest in the nation.

Project Lazarus was an organization responsible for community activation, OEND program implementation, coordination of prevention programs, and surveillance of opioid-related data trends. The Wilkes County Health Department, Chronic Pain Initiative, and Substance Abuse Task Force were involved in educating primary care providers on chronic pain management and safe opioid prescribing practices. Project Lazarus kept record of the opioid overdose interventions along with the year they were implemented (Table 9).

Project Lazarus established OEND programs within physician offices. The physicians were trained to identify patients who could potentially benefit from having a naloxone rescue kit, based on their high overdose risk factors. At the office, patients were shown a 20-minute educational video on recognizing and responding to an opioid overdose. The video also addressed proper storage and disposal of opioid medications, as well as treatment options for drug abuse. The physician office then notified a community pharmacy, and the patient would pick up the naloxone kit for free.

Data for overdose analysis was obtained from the North Carolina State Center for Health Statistics. Unintentional overdoses presenting to the Emergency Department was collected from the North Carolina Disease Event and Tracking and Epidemiologic Collection Tool, while the number of deaths from unintentional overdoses was from the North Carolina Office of the Chief Medical Examiner.

The annualized rate of overdose deaths in Wilkes County from 2004 to 2010, was graphed over time (Figure 2). Furthermore, from 2008 to 2010, overdose decedents were divided into whether a Wilkes County physician had prescribed the drug implicated in their overdose by accessing the Controlled Substances Reporting System program.

Table 9: Overdose prevention efforts in Wilkes County, North Carolina and timeline of implementation from 2005 to 2010.

Implementation	Intervention	
Year	**Community level**	**Physician level**
2005	Community organization and activation	
	Coalition building	
2006	Town hall meetings	
	Prevention education via media	
2007	Prevention education at colleges, churches, organizations, forums	Prescriber educational resources via toolkit program
		Controlled Substance Reporting System
2008	Patient support groups	Prescriber education via one-on-one
		Prescriber education via continuing sessions on pain management
		Policy modification on opioid prescribing in the Emergency Department
		Vetting of pain clinics and facilitation for pain clinic referrals
		Prescriber license disciplinary actions by state medical board
2009	Training of drug diversion law enforcement officers	
	Medication take-back events at police departments	
	Prevention education at schools	
2010	Red Ribbon campaign: labels attached to prescription bags warning not to share	Single prescriber and single pharmacy agreement with patient
	OEND programs	

Inclusion Criteria:

Overdose-related deaths in Wilkes County, North Carolina from 2004 to 2010 were included in the study.

Study Results:

The annualized unadjusted overdose deaths in Wilkes County, North Carolina dropped from 46.6 in 2009 to 29.0 in 2010, per 100,000 population (Figure 2). The remaining counties in North Carolina had an increase in overdose deaths during the same time, therefore the study determined that the decline in Wilkes County indicated a response to the overdose prevention programs. The OEND programs were implemented the same year as the decline in overdoses.

From 2008 to 2010, the number of people who died from the same opioid as they were prescribed by a Wilkes County physician, declined from 82% to 10% respectively. During the same time period, prescriber pain management education and actions against prescriber licenses were implemented, further fostering the idea that overdose prevention strategies may be effective.

FIgure 2: Annualized mortality rates from overdoses in Wilkes County, North Carolina, from 2004 to 2010. [16]

Study Critique:

The study inventoried the multiple levels of community efforts in combating Wilkes County, NC, drug overdose epidemic. An easy to read timeline of the year each intervention was implemented facilitated comparison with annual overdose mortality rates. The study detailed the OEND program training process and access to naloxone, which provided qualitative insight into the patient education provided. Sample size of OEND program enrollment was not

given, limiting the evaluation of its impact. Follow-up data on naloxone use and success was also not addressed.

The greatest weakness of this study was that the results were not adjusted for any confounding variables. As a result, of this raw data, any trends in the outcome must be interpreted with caution. The authors of this study did not address whether further evaluation of the preliminary data will take place in the future.

The focus for establishing prevention programs was directed against the opioid overdose epidemic in Wilkes County, NC, however their reported mortality rates did not specify the drug implicated in the overdose, nor whether they were intentional or unintentional. Although the study stated that the overdose fatalities experienced by the population were almost exclusively due to opioids, further research was performed to discern whether the results were indicative of overall overdoses or opioid-specific overdoses. The North Carolina Department of Health and Human Services website was accessed for values specific to unintentional opioid-related overdose fatalities in Wilkes County during the same time as the study.[16] Opioid-specific data was retrieved and plotted against the unadjusted raw data from the study for comparison (Figure 2). The decline in opioid-related overdoses followed the same trend as the study-reported overdoses following OEND program implementation.

Discussion:

Drug overdoses have alarmingly continued to rise in the United States, with opioids as the leading drug involved in related deaths.[4] The increase in national awareness has resulted in funding for strategies to address nonmedical use and misuse of opioids; however, few quantitative studies have been performed to analyze if these strategies are effective at reducing overdose rates and deaths secondary to nonmedical use and misuse of opioids.[12] Among these efforts, OEND programs have been implemented since 1996 and this study attempts to address their effectiveness at reducing mortality of those that overdose on opioids.[12]

Articles were selected if they contained quantitative data on community mortality rates secondary to opioid-related overdoses. Each of the selected articles focused on a different approach to understanding OEND program effectiveness, providing strength to our study for future suggestions on implementation. The selected studies data was diverse regarding social populations, geographic locations, and OEND program delivery methods (Table 10). Our analysis of the results determined that OEND program implementation is associated with a decrease in opioid-related mortality rates, based on data reported by Walley et al. and Albert et al. The mortality rate in relation to OEND programs was not followed over time in the Rowe et al. study, therefore effectiveness could not be extrapolated.

The Walley et al. study provided strong research that demonstrated communities with OEND program implementation had a significant decline in opioid related deaths, as compared to communities without implementation. Furthermore, the correlation was found to be dose related, as communities with higher OEND program enrollments resulted in a significantly greater reduction in death rates than communities with lower OEND program enrollments. This affirms the effectiveness of OEND program intervention and suggests that maximizing the number of enrollment will foster greater access to resources, reducing opioid-related mortality.

Table 10: Overview of Studies. [12,13,15]

	Walley et al.	Rowe et al.	Albert et al.
Type of Study	Interrupted time series analysis	Retrospective	Retrospective
Setting	State-wide	Urban city	Rural county
Duration of study	2002 to 2009	2010 to 2012	2005 to 2010
Delivery method of education	Group discussions	Classroom Lecture	Video presentation
Source of Naloxone	Public Health Department	Community Group	Pharmacy
Findings	Positive association with OEND implementation and decrease in opioid-related mortality rates. Communities with higher OEND enrollments resulted in a significantly greater reduction in death rates than communities with lower OEND enrollments	Increased incidence of opioid overdose is associated with lower income populations and more drug arrests	Positive association between prevention programs targeting opioid overdose, and the decrease in overdose mortality rates

Another factor influencing access to naloxone, is distance to community OEND programs. The study by Rowe et al. investigated spatial relationships between naloxone reversal events, opioid overdose deaths, and OEND programs. Population demographics were also collected for insight into characteristics of the studied communities. This study was a weakness for current analysis as rates of opioid-related deaths were not followed over time, impeding our ability to measure the effectiveness of OEND program implementation. A suggestion for future research includes data collection over different time periods to analyze trends in mortality. Ideally, information gathered pre- and post- OEND program implementation would provide the most significance for effectiveness. Nevertheless, the results in the article are valuable for understanding population characteristics that should be considered for future OEND program implementation.

The study by Rowe et al. analyzed existing OEND program sites with their census tract location in the City and County of San Francisco, California. The OEND program sites had been placed in areas of historically high opiate death rates, specifically heroin. The census tracts with or adjacent to an OEND program sites were found to have significantly higher income inequality, population density, drug arrests, naloxone reversal events and overdose deaths. This finding is important as it suggests that OEND programs can effectively target and educate

populations at risk for opioid-related mortality. In relation to distance to the OEND program site, both naloxone reversal events and opioid overdose deaths were found to decline with increasing distance; while number of drug arrests and population density increased with increasing distance to the OEND program site. This suggests that both naloxone utilization and opioid-related death are likely to occur in more dense population with increased illicit drug activity. The census tracts with heroin-related overdose deaths were found to be significantly closer to OEND program sites when compared to the census tracts without opioid overdose deaths related to heroin. While this finding was significant, the current study cannot draw conclusion as the OEND program sites were originally located in communities associated with high heroin-related overdose deaths.

With the multivariable negative binomial regression models performed by the Rowe et al. study, naloxone reversals were significantly associated with increasing proximity to OEND program sites and with more census tract drug arrests. This association is significant as it suggests that the OEND program sites are effectively providing education about naloxone and its administration to individuals who live in communities with increased illicit drug activity. When applying the multivariable negative binomial regression model to opioid overdose deaths, there was a significant association between census tract overdose deaths and both increasing number of drug arrests and decreased median income; however, there was no statistically significant association between overdose deaths and distance to nearest OEND program site. This association is important as it suggests that communities with lower income and increased illicit drug activity should be targets for OEND program implementation, but that location of the OEND program site is not factor for reducing opioid-related death.

Lastly, in the study by Albert et al., multiple strategies were implemented to target opioid-related overdoses. During the six-year study, the only decrease in annualized overdose mortality rates was in 2010. When the annualized overdose mortality rates are analyzed with the implementation timeline of opioid prevention strategies, OEND program was implemented during same year as the decline in death rates was observed. In contrast, during the study all other North Carolina counties experienced an increase in overdose mortality rates. An odds ratio of 1.48 was calculated using the overdose death rates in Wilkes County, before and after OEND program implementation (Table 11). The resulting positive odds ratio associates a decline in overdose mortality rates after the implementation of OEND programs; however, a definitive conclusion cannot be made without further evaluation of confounding variables. As the opioid crisis is being collectively combated at different angles, future research should consider concurrent preventatives measures.

There are several limitations as the selected articles used in this study cannot be directly compared. The article by Walley et al. presented the mortality rate as a ratio, and did not provide raw values for their calculations. This impeded statistical comparison with the absolute mortality rates presented in the Albert et al. article. The Rowe et al. study provided data on mortality, however it was averaged over a span of years as a single value rather than a rate. These limitations highlight the need for further research, as few quantitative studies have been published comparing OEND program implementation to opioid-related mortality rates. Finally, use of an observational approach, OEND program implementation cannot be found to cause a reduction to opioid-related mortality rates.

Table 11: Odds ratio of opioid-related deaths in the population of Wilkes County, North Carolina with and without OEND implementation from 2009-2010.

Intervention		Outcome Deaths (per 100,000 population)	
		Yes	**No**
	No OEND*	43	99,957
	OEND*	29	99,971

*OEND = Opioid Overdose Education and Naloxone Distribution

Conclusion:

Among opioid users, does implementation of OEND programs as compared to no OEND program implementation decrease unintentional mortality rates secondary to opioid overdose?

Opioid overdose education and naloxone distribution programs are associated with decreased unintentional mortality secondary to opioid overdose. The implementation of OEND programs varies widely regarding education delivery method, program location, populations targeted, and community partnership. As a result, we recommend that implementation of OEND programs be strategic, community-level efforts that leverage available resources and partnerships to address the national opioid epidemic. Finally, OEND programs should target demographic characteristics that are associated with increased incidence of opioid overdose death, specifically populations with lower median income and increased drug arrests.

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