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POSTMORTEM SCREENING OF OPIOIDS, BENZODIAZEPINES, AND ALCOHOL AMONG RURAL AND URBAN SUICIDE DECEDENTS

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Abstract

Purpose: Fatal suicides involving opioids are increasingly common, particularly in rural areas. As co-use of opioids with other substances contributes significantly to mortality risk, we examined whether positive screens for opioids with other substances is more prevalent among rural versus urban suicide deaths, as this could have implications for public health strategies to reduce overdose suicides.

Methods: Data from all states reporting opioid-related overdose suicides in the National Violent Death Reporting System (NVDRS) from 2012–2015 were used. Relative risk ratios were obtained using multinomial logistic regression, comparing opioid-only to 1) opioid and alcohol, 2) opioid and benzodiazepines, and 3) opioid, alcohol, and benzodiazepines suicides across rurality. Models were fit using robust standard errors and fixed effects for year of death adjusting for individual, county, and state-level covariates.

Findings: There were 3,781 opioid-overdose suicide decedents (42% female) tested for all three substances during the study period. Unadjusted prevalence of positive screens in decedents varied across rurality (p=0.022). Urban decedents were more likely to test positive for opioids alone while rural decedents were more to likely test positive for opioids and benzodiazepines.

Conclusions: Rural suicides are associated with increased opioid and benzodiazepine positive screens. These findings suggest the need for rural-focused interventions to support appropriate

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Disclosure of Interest: This research uses data from NVDRS, a surveillance system designed by the Centers for Disease Control and Prevention's (CDC) National Center for Injury Prevention and Control. The findings are based, in part, on the contributions of the 42 funded states and territories that collected violent death data and the contributions of the states' partners, including personnel from law enforcement, vital records, medical examiners/coroners, and crime laboratories. The analyses, results, and conclusions presented here represent those of the authors and not necessarily reflect those of CDC. Persons interested in obtaining data files from NVDRS should contact CDC's National Center for Injury Prevention and Control, 4770 Buford Hwy, NE, MS F-64, Atlanta, GA 30341–3717, (800) CDC-INFO (232–4636). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institute on Alcohol Abuse and Alcoholism, the National Institutes of Health, CDC, or the American Public Health Association. The authors report no conflicts of interest.

co-prescribing, better health education for providers about risks associated with drug mixing, and more linkages with mental health services.

Keywords

suicide; rural; urban; multiple drug use

INTRODUCTION

Opioid overdose deaths tripled in the United States over the last twenty years, with over 30,000 opioid-related overdose deaths in 2015,[1] while suicide deaths have also increased during this time.[2] Recent studies show that co-use of opioids, benzodiazepines, and alcohol is common[3–5] and increases risk of fatal overdoses.[5–8] Opioid use and co-use with benzodiazepines is also associated with increased suicide risk.[9] Suicide risk is generally higher in rural areas,[10] where opioid overdose rates initially rose more steeply compared to urban areas.,[11] Although some research suggests that suicide mortality associated with multiple substance co-use may be greater in rural than urban areas,[12,13] studies have not explicitly examined this.

Importantly, opioid use is associated with increased suicide risk. People who use heroin have 14 times higher risk of fatal suicide relative to people who do not use heroin,[6] and higher prescription opioid doses are associated with greater suicide risk.[14] Among those reporting opioid use, benzodiazepines co-use is a strong predictor of suicide attempts[9] and is often involved in non-fatal opioid-related drug overdoses.[15] In 2014, 27.9% of all suicide decedents tested positive for acute alcohol intoxication, 32.6% for benzodiazepines, and 30.0% for opioids.[16] The percentage of suicides involving all three substances, relative to use of opioids alone, is unknown. Alcohol and benzodiazepines, like opioids, increase opioid respiratory insufficiency,[17] leading to increased mortality risk when used along with opioids. In addition to co-prescribed use for co-occurring conditions (e.g. anxiety and chronic pain), benzodiazepines may be used non-medically to reinforce effects of opioids.[18]

In rural areas, opioid overdose rates have recently risen more rapidly than in urban areas, with an 84% increase in rural areas and 61% increase in urban areas between 1999–2015,[11] although opioid and drug overdose death rates are higher in urban relative to rural counties.[19,20] Notably, the availability of fentanyl and other high potency opioids, thought to be a major driver of increasing drug overdose mortality rates nationwide, are not as strongly associated with overdose mortality in rural counties as they are in urban counties.[21] While there is significant heterogeneity in opioid use and related mortality within rural counties across the United States,[22,23] some evidence suggests that rural mortality by suicide involving more than one substance may be higher than in urban areas. For instance, greater opioid and benzodiazepine use and availability have been found in some rural areas[13] and geographic hotspots,[24] and one study found that the majority of rural individuals using opioids also report lifetime benzodiazepine use.[25] In addition, among male suicide decedents, acute alcohol intoxication at time of death was found to be more common among rural relative to urban men.[12] Importantly, rural areas often lack access to sufficient overdose prevention (i.e. naloxone) and mental health or substance use treatment services,

which may contribute to the increased mortality risk among overdoses in rural areas.[23,26,27] Given evidence of increased use and possible co-use in some rural (vs. urban) areas, along with decreased treatment options to prevent deaths by suicide, it is plausible that deaths involving opioids as well as benzodiazepines and alcohol may be higher in rural areas than in urban areas.

Compared to an extensive literature on opioid overdoses or any-drug overdoses, little is known about the factors associated with multiple-drug involved overdose deaths,[5] particularly among suicide decedents. While co-use is common and known to be associated with mortality, it is unknown which factors predict co-use of opioids and other substances (vs. opioids alone) among suicides. Yet better understanding factors associated with use of multiple drugs among fatal suicide may provide important recommendations for prevention.

The challenges of studying co-use related suicide deaths, or overdose deaths more broadly, may be one reason for the sparse literature on co-use related mortality. Specific-drug death is difficult to examine across states or jurisdictions given differences in autopsies and toxicology testing across states with different death investigation systems,[12,28,29] which results in differences in how drug-related cause of death is classified on the death certificate. Addressing these difficulties, the National Violent Death Reporting System (NVDRS) in a national dataset includes toxicology reports for suicide decedents, making this dataset useful for studying combinations of alcohol and substances present among overdose suicide decedents.[30,31]

The aim of this exploratory study was to describe the prevalence of benzodiazepine and alcohol positive postmortem toxicology screens among opioid-involved overdose suicide decedents and specifically to compare this prevalence of multiple substance use related deaths across rurality, adjusting for potential confounders. Additionally, this study explores other key individual and community-level factors and whether these are associated with co-use suicide deaths independent of rurality.

METHODS

This study was determined to be exempt from institutional review board review by the University of California Berkeley Office for Protection of Human Subjects.

Data Source:

Data from the National Violent Death Reporting System (NVDRS) were used in this study. NVDRS is the only state-based surveillance system that pools data on violent deaths from multiple sources, including death certificates, coroner/medical examiner (CME) reports, and law enforcement reports. NVDRS collects and links data from these different sources, which are abstracted and entered in NVDRS. Description of NVDRS has been published elsewhere.[16]

Given differences in classifying suicides and undetermined deaths across jurisdictions that could be associated with rurality,[32] particularly among drug-related deaths,[33] only deaths determined to be suicides were included in this study. All included decedents had opioid-

related overdose listed as a cause of death, defined using both toxicology reports and cause of death determination from the medical examiner or coroner. As NVDRS does not specify type of opioid, this measure included all decedents testing positive for any opioids (including those obtained illicitly and those prescribed to the decedent). Given differences in death reporting systems[28,34] and toxicology reporting,[12,29] decedents were included that had been tested for opioid, alcohol, and benzodiazepine use and who had tested positive for opioid use.

NVDRS data collection began in 2003 with seven states; six states joined in 2004, four in 2005, and two in 2010. In 2015, NVDRS expanded to include 14 additional states for a total of 32 states in the system. In this study, data were included from 27 states having at least one death meeting inclusion criteria during the study period: Alaska, Arizona, Colorado, Connecticut, Georgia, Hawaii, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Rhode Island, South Carolina, Utah, Vermont, and Virginia. The time period for this study was 2012–2015 to maximize the amount of data reported, as few deaths with toxicology reports for all three substances were reported prior to 2012 (n=109). Data were also limited to those reports with a valid residential county.

Screening positive for multiple substances at time of death:

Substance use at death was defined as: 1) positive screen for opioid-only, 2) positive screen for opioid and alcohol, 3) positive screen for opioid and benzodiazepine, and 4) positive screen for opioid, benzodiazepine, and alcohol. Like opioid use, alcohol use and benzodiazepine screens were determined by toxicology reports for decedents, defined as a positive test at time of death. Toxicology tests reported to NVDRS do not include information about the type of opioids (such as heroin or Vicodin), alcohol (such as wine, spirits, or beer), or benzodiazepines (such as Xanax) found, nor about the dosage of opioids or benzodiazepines. Therefore, opioids, alcohol, and benzodiazepine screens were measured dichotomously based on the toxicology screening test (any vs. none). Cause of death data derived from the death certificate was not used as a primary way to establish co-use at time of death because testing and reporting of substances on the death certificate can vary depending on subjective criteria such as the state death reporting system procedures,[35] and individual lab processes.[36]

Rurality:

Rurality was defined using decedent's county of residence at time of death. 2013 Rural-Urban Continuum Codes (RUCC) were used, based on the Office of Management and Budget metropolitan and non-metropolitan categories.[37] Rurality was operationalized as urban (metropolitan) and rural (non-metropolitan).

Covariates:

Several covariates were also included in this study and entered into models sequentially to examine whether their inclusion attenuated rural-urban differences in multiple drug use-related mortality. Individual-level covariates were derived from NVDRS data, while county-

level covariates were derived from the 2010 Census data, linked by decedent county of residence. Individual-level demographic factors such as gender, race/ethnicity, homelessness, and education were included as these are associated with substance use patterns both among living populations[38,39] and among suicide decedents, patterns which vary across rurality.[12,40] Year of death was included to account for differences in reporting states, toxicology screening practices, and counties included by year (due to rarity of suicides).

Substance use problems were included to control for problem severity, which varies across rurality,[41] and were dichotomous variables based on information reported in the coroner/medical examiner (CME) report and included in NVDRS. Presence of an alcohol problem was endorsed if decedent participated in an alcohol rehabilitation program or reports of regular alcohol use around time of death. Presence of substance use problems was endorsed if decedent participated in drug rehabilitation programs or reports of regular substance use around time of death. Both alcohol and substance use problem variables were based on current use at time of death, not lifetime use.

Mental health variables (mental health problems and history of mental health treatment) were also included as they are strongly associated with suicide risk and substance use.[42] Mental health problems were dichotomous variables based on information in the CME report and included in NVDRS, and endorsed if the decedent had a disorder or syndrome listed in DSM-IV, or if the decedent was being treated for a mental health problem through involuntary mechanisms, was currently in mental health treatment for an unresolved problem, or was prescribed a psychiatric medication at time of death. History of mental health treatment was endorsed if the CME report included lifetime reports of the decedent seeing a mental health professional for a substance use or mental health problem in any setting, receiving a psychiatric prescription, or residing in a mental health treatment facility.

County-level poverty, operationalized categorically by quartiles of household poverty from 2010 Census data, was included as a covariate as this is associated with substance use patterns,[43] suicide risk, [44] and rurality.[45] Two additional variables were included to account for state-level differences that may confound the association between rurality and co-use. We controlled for state death reporting systems as these determine resources available for toxicology testing and reporting[35] and can vary within states that have county-level medical examiners or coroners. The presence of any state-level naloxone laws to increase naloxone availability (e.g. through pharmacy availability, good Samaritan laws, or other laws) was included as a dichotomous variable for the year of death to account for state differences in accessibility of naloxone to people who use opioids, an important factor in overdose prevention. [46]

Finally, region (defined by four US Census regions) is associated with both the pattern and reporting of substance use.[41] Alcohol use patterns and opioid overdose deaths are not uniformly distributed across regions: alcohol use is more common in the Midwest[41] and the type of opioid involved in overdoses (synthetic opioids versus heroin) varies across region.[1] However, given limitations to the reporting states not representing all states in all regions, we did not include this in the analytic model, but only describe regional differences across all outcomes.

Analytic Strategy:

The proportion of overdose suicide victims who screened positive for 1) opioid use only, 2) opioid and alcohol, 3) opioid and benzodiazepine, and 4) for all three substances were described across rurality and compared using chi-square tests of independence, overall and with pairwise comparisons using a Bonferroni correction to account for multiple comparisons.[47] All descriptive characteristics were compared overall with chi-square tests. Relative risk ratios comparing screening positive for multiple substances (vs. opioid use alone) between urban and rural overdose suicide decedents were assessed using a multinomial logistic regression model, comparing opioid-only to 1) opioid and alcohol, 2) opioid and benzodiazepines, and 3) opioid, alcohol, and benzodiazepines. Models were fit using robust standard errors and fixed effects for year of death. Multiple models were ran, including 1) an unadjusted model, and 2) a model adjusted for individual-level covariates, and 3) models adjusted additionally for each county and state level covariate. Using the fully adjusted model, the significance of all variables was also assessed. All analyses were done with Stata v15.[48]

Inclusion in Analytic Sample:

Opiate, alcohol, and benzodiazepine screening were described across all suicide decedents between 2012–2015, but specific criteria were used to create the analytic sample in response to the research question. The analytic sample included only suicide decedents between 2012–2015 who had been screened for all three substances, screened positive for opiates, and had opiates listed as a cause of death. Of 170,758 suicide and undetermined deaths reported to NVDRS between 2003–2015, virtually all (>99.9%) of decedents had a reported state and county of death corresponding to a 2013 RUCC code (n=169,743). Of these decedents, 40.9% (n=69,506) died between 2012–2015. Of those who died between 2012 and 2015, 29.9% were screened for all three substances and included in this study (n=20,802). Of those tested for all three substances, 27.9% screened positive for opioids (n=5,796), and of those screened positive for opioids, 67.0% were confirmed suicides (n=3,885). Of the suicide decedents testing positive for opioid use, 97.3% were overdose deaths, or had opioid use listed as a cause of death (n=3,781). Therefore, 3,781 suicide decedents were included in the analytic sample.

RESULTS

There were 60,933 suicide deaths from reporting states between 2012–2015 with reported county of residence. Of these, 39.8% were tested for opiates (n=24,250), 55.0% were tested for alcohol (n=33,488), and 33.7% (n=20,549) were screened for Benzodiazepines. Among those screened for opiates, 26.6% screened positive for opiates (n=6,454), including 27.1% of those in urban areas (n=5,486) and 26.7% of those in rural areas (n=1,059). Among those screened for alcohol, 39.0% screened positive for alcohol, including 39.0% in urban areas (n=10,826) and 28.5% in rural areas (n=2,221). Among those screened for benzodiazepines, 31.5% screened positive for benzodiazepines (n=6,482), including 31.3% in urban areas (n=5,440) and 32.5% in rural areas (n=1,042).

Given that NVDRS did not include all states during this time, a comparison of urban-rural differences in opioid poisoning suicides was conducted with data from CDC WONDER.[49] Specifically, data from 2012–2015 for all decedents in the United States with multiple causes of death classified including both T40 (opioid poisoning) and X60-X84 (intentional self-harm) were compared across rurality to NVDRS data in the analytic sample. Among all decedents meeting these criteria in the United States (n=7,368), 85.6% resided in a metro area (n=6,310) and 14.4% resided in a nonmetro area (n=1,056). The breakdown was similar in the NVDRS analytic sample (n=3,781), in which 83.7% of decedents were urban (n=3167) relative to 16.2% of decedents being rural (n=614).

As shown in Table 1, among the 3,781 suicide decedents included in the analytic sample, there were statistically significant differences in prevalence of substance use in decedents across rurality overall (p=0.022), although not between all groups. While 32% of rural decedents screened positive for opioids only, 36% of urban decedents screened positive for opioids only. In pairwise comparisons, one significant difference across rurality was found, with 41% of rural decedents screening positive for a combination of opioids and benzodiazepines, in contrast to 34% of urban decedents (p = 0.007). Screening positive for alcohol and opioids, and screening positive for alcohol, opioids, and benzodiazepines (relative to opioids alone) were not significantly different. Rural decedents were also more likely to be white, have a high school education or lower, to live in a higher poverty county, and to live in a county with either a county-based mix of death investigations systems, a centralized state medical examiner, or a county coroner.

In unadjusted models and models adjusted for individual-level factors, rural suicide decedents were 35% more likely to screen positive for opioids and benzodiazepines (vs. opioids alone) relative to urban suicide decedents (RRR adjusting for individual level factors =1.35, 95% Confidence Interval (CI) = 1.10, 1.67; Table 2). Importantly, this association was attenuated after adjusting for community-level poverty (Table 2). Screening positive for both alcohol and opioids and for all three substances were similar across rurality in all models.

In further analysis, as shown in Table 3, several significant factors were found to be associated with screening positive for alcohol, opioids, and benzodiazepines. There were a few notable findings related to opioid and benzodiazepine positive screens that may help explain rural-urban differences. Opioids and benzodiazepines (vs. opioids alone) was higher among women, white decedents (vs. Hispanic), those with a current mental health or substance use problem, decedents in higher-income communities, while lower in later years.

4. DISCUSSION

This study explores differences in use of alcohol, benzodiazepines, and opioids at time of death among suicide decedents who died from an opioid overdose. Our results extend previous studies that have established an association between co-use and increased mortality risk by considering whether multiple-substance related mortality varies across rural and urban areas. In this study we found differences in substance use (measured by toxicology screening at time of death) across rurality among suicide decedents. Specifically, opioid and benzodiazepine positive screens was found to be an important substance use combination

contributing to mortality in rural areas. Further, this difference was largely explained by community-level factors.

Compared to urban suicide decedents, rural decedents were more likely to screen positive for opioids and benzodiazepines (vs. opioids alone). This was found in bivariate analyses and after adjusting for individual-level factors and community-level factors. This is consistent with rural-urban differences in reported co-use among living persons and non-suicide specific decedents. For instance, co-use of opioids and benzodiazepines was found to be higher in rural relative to urban decedents in one study in Virginia,[50] and non-medical use of prescription drugs has been found to be higher in rural areas relative to urban areas.[13] However, differences were attenuated when adjusting for poverty. Interestingly, there were no differences across rurality in risk of screening positive for opioids and alcohol nor opioids, alcohol, and benzodiazepines.

These findings of rural-urban differences in the detection of multiple substance use among suicide decedents may reflect trends in non-medical use, as well as reflecting broad rural-urban differences in access to mental health care. A qualitative study of reasons for polysubstance use suggests this is commonly done for self-medication of mental and physical health conditions.[51] Previous research has indicated rural patients are less likely to receive office-based mental health care[52] but are more likely to receive pharmacotherapy for mental health problems.[53] This may explain increased benzodiazepine co-use associated with rural opioid overdose suicide. Increased co-prescribing may also be an unintended consequence of integration of behavioral healthcare in primary care clinics in rural areas.[53,54] However, urban-rural differences remain after adjustment for a history of mental health treatment and current mental health problems, indicating this finding is not fully explained by differences in receipt of mental health treatment.

Observed rural-urban differences in opioid and benzodiazepine involved deaths were attenuated after adjusting for poverty. Findings related to poverty are complex, as suicide deaths were associated with opioid and benzodiazepine positive screens in communities with *less* poverty (relative to those with the most poverty); however, decedents in *rural* areas were more likely than urban areas to be in the highest quartile of poverty (46% of rural decedents relative to 11% of urban decedents). It may be that some of this complexity represents differences in county-level racial/ethnic composition. As white people have a higher rate of opioid overdose nationwide than the largest other racial/ethnic groups[11] and rural racial/ethnic minorities are more likely to experience poverty,[55] it is possible that rural counties with a higher proportion of racial/ethnic minorities may experience fewer drug-related suicides while experiencing increased poverty. This warrants additional research, as previous studies on rural drug overdose found counties with high poverty to have higher mortality rates,[20–22,56,57] although one recent pilot study examining social determinants predicting opioid and benzodiazepine co-use among patients found socioeconomic factors including poverty and unemployment were not predictive of co-use.[24]

Broader research on overdose mortality suggesting overdose risk varies across rural communities related to community-level factors, including region.[21–23] In this study there were regional differences in prevalence of rural-urban suicide among states included in the

analytic sample. Given limitations of reporting states in this sample, regional comparison of deaths was not possible. However, previous studies that found higher rates of co-prescribing of opioids and benzodiazepines, [58] inappropriate prescribing,[59] and prescription of benzodiazepines even when not clinically recommended[60] in rural areas in the South. As NVDRS expands to include all states, future research on co-use and suicide using data from all states should examine regional differences and explore additional community factors.

We tested additional demographic and mental health factors hypothesized to be associated with co-use. Notably, both screening positive for opioids and benzodiazepines, and opioid, alcohol, and benzodiazepines was associated with higher suicide risk (vs. opioids alone) for women (vs. men), and lower risk in non-white (vs. white) decedents. These findings may reflect co-use patterns in these important subpopulations.[58] Findings that use of multiple substances was related to substance use and mental health problems and history of mental health treatment was unsurprising.

Opioid and benzodiazepine positive screens were less common in later years than in 2012, which may reflect decreased co-prescribing and increased availability of high potency opioids, although synthetic opioid involvement in multiple drug overdoses also increased over this time.[61] Increases in availability of high potency opioids may be because of changes to opioid prescribing guidelines and creation of prescription drug monitoring programs in many states.[62,63] Findings of differences across death investigation systems were surprising, as decedents included in this study all had a toxicology report for all three substances assessed, but may reflect differences in approach to assessing multiple substance use related mortality. Future research is needed to compare when and how different state death investigation systems determine the need for toxicology reports, the types of toxicology tests used, and more detailed toxicology information among those suspected of overdose.

While this study makes important contributions identifying factors associated with use of multiple substances at time of death among suicide decedents, there are number of significant limitations. Suicides may be underreported due to the difficulty in ascertaining intention among overdose deaths.[33] Similarly, many overdose deaths do not specify classification of drug involved in death, and thus this study undercounts drug overdose deaths.[64] As this study was limited to NVDRS participating states and decedents with a toxicology report for all three substances of interest, findings are not generalizable to non-NVDRS states or suicide decedents without toxicology reports (70% of deaths reported to NVDRS during the study period). However, this study improves on previous studies relying on death certificates or single state analysis by using toxicology screening data from many states. While only decedents with toxicology reports for all three substances of interest were included in this study to allow comparison across rurality, there may be jurisdictional-level differences in the types of toxicology tests used that may bias results.[29] Additionally, the toxicology reports in NVDRS do not include type of opioids, benzodiazepines, or alcohol found, nor the dosage for opioids or benzodiazepines. Future work focused on whether co-use patterns are similar with different types of opioids (i.e. prescription opioids, heroin, and fentanyl) and to identify dosing associated with multiple substance use fatalities. This study is also not generalizable to undetermined or non-intentional deaths. Some factors that may account for differences across rurality in co-use patterns (such as type of opioid used,

level of toxicity, and medical or non-medical prescription drug use), are not available in NVDRS, resulting in unmeasured confounding. Given the number of states reported and the small sample sizes for certain states, state fixed effects were not possible. Therefore, there may be additional unmeasured state-level confounding that is not addressed in this study.

CONCLUSIONS

This study makes important contributions to understanding factors associated with multiple substance use related suicides. Rurality was associated with increased risk of opioid and benzodiazepine positive postmortem screening. Additionally, key factors including gender, race, and co-morbid mental health or substance use, and community-level poverty are associated with differential co-use related suicide risk. Future work is needed to better understand what specific combinations of different types of opioids, alcohol, and benzodiazepines are associated with mortality and the ways in which these substances contribute to specific mechanisms of death in combination, details which are essential to guiding potential intervention efforts. NVDRS has recently expanded to all states, which will provide a larger dataset in which to examine these patterns for future study. In particular, future studies should examine sub-national differences in rural-urban drug involved suicide, such as regional differences. Additional research is also needed to understand the effects of policies and interventions on mortality overall and specifically on suicides in rural areas. Research in rural areas is needed on additional strategies to prevent mortality from overdose for both suicides and unintentional overdose.

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Data Availability:

The data that support the findings of this study are available from the CDC. Descriptive data can be accessed free of charge from NCIPC's Web-based Injury Statistics and Query System (WISQARS). More detailed data from the NVDRS Restricted Access Database (RAD) is available by request for users meeting certain eligibility criteria. More details are available here: https://www.cdc.gov/violenceprevention/datasources/nvdrs/datapublications.html

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Table 1:

Descriptive Characteristics for all covariates across rurality for suicide decedents in participating NVDRS states from 2012–2015 (n=3,781)

		Rural (n=614)		Urban (n=3,167)		
		%	N	%	N	p-value
Outcome based on Toxicology Reports	Opioids only	32.3	198	35.8	1,134	0.020
	Opioids + Alcohol	12.2	75	13.6	429	
	Opioids + Benzos	40.6	249	33.9	1,075	
	Opioids, Alcohol + Benzos	15.0	92	16.7	529	
Gender	Female	43.5	267	41.1	1,311	0.275
	Male	56.5	347	58.9	1,880	
Race/ Ethnicity	White	94.3	579	90.0	2,850	0.001
	Black	1.1	7	2.9	92	
	Hispanic	1.6	10	4.3	137	
	Other	2.9	18	2.8	88	
Homeless	Yes	1.0	6	1.3	41	0.481
	No	96.1	590	96.5	3,055	
	Unknown	2.9	18	2.2	71	
Education	< HS	13.5	83	8.2	259	<0.001
	HS diploma/GED	35.0	215	29.0	919	
	Some college	21.7	133	20.7	655	
	Bachelors +	9.8	60	13.9	439	
	Unknown	20.0	123	28.3	895	
Current Mental Health problem		50.0	307	56.5	1,789	0.003
History of Mental Health Treatment		42.7	262	49.5	1,568	0.002
Alcohol Problem		13.8	85	17.7	560	0.021
Other Substance Use Problem		38.3	235	35.3	1,117	0.155
Quartiles of Community Level Poverty	3.3% – 9.4% in poverty	11.1	68	31.5	999	<0.001
	9.5% – 13.4% in poverty	24.4	150	30.7	973	
	13.5% – 16.4% in poverty	18.2	112	26.3	833	
	16.5% – 40.5% in poverty	46.3	284	11.4	362	
Naloxone Law at time of death		50.1	310	54.0	1,710	0.111
State Death Reporting System	County-based mix	18.9	116	16.0	506	<0.001
	Centralized ME	52.8	324	49.8	1,577	
	County ME	1.3	8	15.3	485	
	County Coroner	27.0	166	18.9	599	

		Rural (n=614)		Urban (n=3,167)		
		%	N	%	N	p-value
Region	Northeast	4.7	29	28.8	911	<0.001
	Midwest	17.4	107	11.5	364	
	South	50.2	308	25.4	803	
	West	27.7	170	34.4	1,089	
Year of Death	2012	17.9	110	15.0	476	0.328
	2013	21.7	133	22.5	714	
	2014	25.6	157	27.2	860	
	2015	34.9	214	35.3	1,117	

Table 2:

Relative risk ratio of rural relative to urban co-use (vs. use of opioids alone) based on multinomial models for suicide decedents in participating NVDRS states from 2012–2015 (n=3,781)

	Opioids only	Opioids+Alcohol RRR (95% CI)	Opioids+Benzos RRR (95% CI)	Opioids+Alcohol+Benzos RRR (95% CI)
Unadjusted	Base outcome	1.00 (0.75, 1.34)	1.33** (1.08, 1.63)	1.00 (0.76, 1.30)
Adjusted for individual level factors	Base outcome	1.08 (0.80, 1.45)	1.35** (1.10, 1.67)	1.03 (0.78, 1.37)
Adjusted additionally for naloxone prescribing laws	Base outcome	1.08 (0.80, 1.45)	1.35** (1.10, 1.67)	1.04 (0.78, 1.37)
Adjusted additionally for death reporting system	Base outcome	1.11 (0.82, 1.50)	1.34** (1.08, 1.66)	1.09 (0.81, 1.45)
Adjusted additionally for poverty level	Base outcome	0.99 (0.72, 1.36)	1.22† (0.97, 1.54)	0.91 (0.67, 1.23)

† significant at p<0.1

* significant at p<0.05

** significant at p<0.01

Adjusted for individual level factors = adjusted for gender (male/female), age (continuous), race (white, black, Hispanic, other), homeless status, education (< high school, diploma/GED, some college, bachelor's or higher), current mental health problem, history of mental health treatment, current alcohol problem, current substance abuse, year of death

Adjusted additionally for community level factors = adjusted individual level factors as well as 1) whether there was a state-level naloxone prescribing law at time of death, 2) state death reporting systems (county-level mixed ME and coroner, centralized ME, county-level ME, county-level coroner), and 3) quartiles of community-level poverty (based on Census estimates of % adults in poverty)

Table 3:

Relative Risk Ratio of all covariates for co-use (vs. opioids alone) among suicide decedents in participating NVDRS states from 2012–2015 (n=3,781)

		Opioids+Alcohol RRR (95% CI)	Opioids+ Benzos RRR (95% CI)	Opioids+Alcohol+ Benzos RRR (95% CI)
Rural (vs. urban)		0.99 (0.72, 1.36)	1.22 † (0.97, 1.54)	0.91 (0.66, 1.23)
Female (vs. male)		0.95 (0.76, 1.20)	1.72 *** (1.46, 2.03)	1.56 *** (1.27, 1.93)
Age		0.98 *** (0.98, 0.99)	1.00 (0.99, 1.00)	0.99 * (0.99, 1.00)
Race/ Ethnicity	White		reference	
	Black	1.63 (0.91, 2.93)	0.86 (0.51, 1.44)	0.66 (0.33, 1.35)
	Hispanic	0.91 (0.57, 1.44)	0.44 *** (0.28, 0.69)	0.29 ** (0.15, 0.55)
	Other	1.10 (0.61, 1.96)	0.62 † (0.37, 1.02)	0.64 (0.34, 1.19)
Homeless		1.04 (0.96, 1.12)	1.05 (0.98, 1.11)	1.10 ** (1.03, 1.18)
Education	< HS		reference	
	HS diploma/GED	1.25 (0.84, 1.87)	0.83 (0.61, 1.12)	0.97 (0.67, 1.42)
	Some college	1.13 (0.74, 1.73)	0.76 (0.561, 1.05)	1.01 (0.68, 1.50)
	Bachelors +	1.34 (0.84, 2.13)	0.97 (0.68, 1.38)	1.22 (0.79, 1.89)
	Unknown	1.33 (0.86, 2.05)	1.02 (0.74, 1.42)	1.12 (0.75, 1.69)
Current Mental Health problem		0.68 * (0.48, 0.95)	1.52 ** (1.18, 1.97)	1.62 ** (1.18, 2.21)
History of Mental Health treatment		1.23 (0.86, 1.76)	1.29 † (0.99, 1.66)	0.81 (0.59, 1.11)
Current Alcohol problem		5.09 *** (3.89, 6.66)	0.85 (0.65, 1.11)	4.37 *** (3.37, 5.65)
Current Substance Use problem		0.68 ** (0.53, 0.87)	1.22 * (1.02, 1.45)	0.88 * (0.70, 1.10)
Year of Death	2012		reference	
	2013	0.88 (0.60, 1.30)	0.73 * (0.56, 0.95)	0.94 (0.67, 1.32)
	2014	1.17 (0.75, 1.82)	0.65 * (0.48, 0.89)	1.12 (0.76, 1.65)
	2015	1.29 (0.79, 2.10)	0.63 * (0.44, 0.90)	1.04 (0.69, 1.59)
Quartiles of Community Level Poverty	1st (Least poverty)		reference	
	2nd	0.92 (0.69, 1.22)	0.72 ** (0.58, 0.89)	0.92 (0.70, 1.22)
	3rd	0.94 (0.69, 1.27)	0.81 † (0.61, 1.15)	0.93 (0.70, 1.25)
	4th (Most poverty)	1.35 (0.95, 1.92)	1.02 (0.76, 1.37)	1.47 * (1.04, 2.08)
Naloxone Law at time of death		0.95 (0.69, 1.31)	1.23 † (0.97, 1.57)	0.75 * (0.57, 0.99)
State Death Reporting System	County-based mix		reference	

		Opioids+Alcohol	Opioids+ Benzos	Opioids+Alcohol+ Benzos
		RRR (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**
	Centralized ME	0.76 (0.56, 1.04)	0.90 (0.70, 1.14)	0.54 *** (0.40, 0.72)
	County ME	1.08 (0.74, 1.58)	0.84 (0.61, 1.15)	1.05 (0.74, 1.50)
	County Coroner	0.99 (0.69, 1.43)	1.02 (0.76, 1.37)	0.88 (0.62, 1.26)

† P < 0.1

* P < 0.05

** P < 0.01

*** P < 0.001