Preliminary Report

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Overdose mortality rates following the introduction of naloxone rescue kits

Abstract

Background: Opioid addiction remains a major public health problem bearing enormous societal costs including death by overdose in about 90 Americans every day. The increase in opioid mortality rate over the past few years has been attributed to multiple factors, including overprescribing of prescription opiates, the emergence of high potency opioid forms (i.e., fentanyl- and carfentanyl-laced heroin) and lack of sufficient rehabilitation and other treatment modalities. Naloxone rescue is an intervention ready to be evaluated.

Aim: To determine whether there was a decrease on opioid deaths in two New Jersey counties after the introduction of naloxone rescue kits.

Results: After an initial decrease in opioid-related death following the introduction of naloxone rescue kits, the death rates again climbed in both jurisdictions.

Conclusion: While naloxone did show some promise in stemming opioid-related mortality, factors such as the availability of fentanyl and, perhaps, a false sense of security drove mortality rates upwards during the second year. Further research is needed to better delineate long-term solutions to opioid-related mortality.

Keywords: opiate-related mortality, naloxone, opiates, drug addiction

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Alton J Appleton,[1] Adenike Animasaun,[1] Karim Sedky,[1] Igor Elman,[1] Andres Pumariega[2]

1Department of Psychiatry, Cooper Medical School of Rowan University, USA

2Division of Child and Adolescent Psychiatry, University of Florida College of Medicine, USA

Correspondence: Karim Sedky, Psychiatry Medical Student Clerkship Director, Department of Psychiatry, Cooper Medical School of Rowan University, Camden, NJ 08103, 401 Haddon Ave, Suite 346, E and R building, USA, Tel 856-757-7799, Fax 856-757-7799, Email sedky66@hotmail.com

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Abbreviations: FDA, food and drug administration; EMS, emergency medical personal; DOPE, drug overdose prevention and education project; IRB, institutional review board; cART, combination antiretroviral therapy; HIV, Human immuno-deficiency virus; CDC, center for disease control; DEA, drug enforcement agency

Introduction

Background

Substance-related mortality rate has been increasing in the United States (US) and in various parts of the world. Analysis of drug-related death rate in the US revealed that prescriptions for the most common opioids continued to increase in 2014, accounting for 61% of drug overdose deaths among 47,055 individuals.[1] Analysis of drug-related mortality for 2015 showed a decrease in methadone-related mortality, but a significant increase in heroin (a spike from 10,574 in 2014 to 12,989 in 2015) and other synthetic opioid-related mortality.[2,3] The drug-related mortality rate increased from 47,055 in 2014 to 52,404 in 2015 and opioids were responsible for 60.9% and 63.0% of the mortality rate respectively in the two years. Among 51 states, death rate increased from 9.0/100,000 in 2014 to 10.4/100,000 in 2015.[1]

The US drug-related mortality trend also highlighted that deaths by natural/semisynthetic opioid increased by 2.6%, compared to deaths by heroin, which increased by 20.6% and synthetic opioid, which increased by 72.2% from 2014 to 2015.[1] Demographics of people addicted to opioids showed a dramatic change over the last 50 years, from, in the 1960s, involving young males (82.8% with mean age 16.5 years old) from low socioeconomic status, with no ethnic predominance and initiating their addiction through heroin use (80%), to the current demographics: mainly middle class Caucasian adults (mean age 22.9).[4] Female use and initiation of addiction through prescription drugs (75%) also significantly increased. This latter change in pattern and occurrence in this opioid epidemic has been mainly attributed to increased opioid prescribing behaviors, use of higher medication dosage, more potent formulations, and limited monitoring. In a study conducted on veterans from 2004 to 2008, fatal opioid overdose was found in 0.04%, with a positive relation to the dose prescribed, especially once the dose reached 50 mg/day or more morphine equivalence.[5]

Camden, NJ is one of the poorest areas in the US, representing a top crime-infested area. Foo et al.[6] indicated an ascending trend in drug overdose-related mortality in Camden between 2010 and 2013, coinciding with the national data showing a dramatic increase in drug-related mortality.[6] In 2010 to 2011, the death rate rose significantly by 45% from 89 deaths in 2010 to 129 in 2011. A less dramatic increase of 7.7% (i.e., n=139) occurred between 2011 and 2012; and by 14% between 2012 and 2013 (i.e., n=159). However, a decline by 13% (i.e., n=138) occurred from 2013 to 2014. Similarly, in Gloucester County, 40 individuals died in 2010 secondarily to drugs compared to 50 in 2011 (data obtained from health department). This increase in death rate in Gloucester County continued at 57 for 2012 and 71 in 2013.

Although several settings and treatment modalities exist for people struggling with addiction, especially when related to opioids, access to these modalities remains limited. In a Canadian study examining youths using street drugs, lack of access to addiction treatment predicted the switch to parenteral drug addiction: 41% attributed the shift to lack of access to detoxification, 35% reported lack of treatment

centers, 10% reported lack of recovery house and 4% reported lack of counseling services.[7] Medication-assisted treatments have proven to be beneficial in opioid addicted individuals; however, the limited access to treatment, whether due to the unavailability of providers or lack of insurance coverage, is a major obstacle. While major efforts have been focused on educating physicians about the risks and how to better assess addiction potential prior to prescribing controlled substances, more is needed to address the limited insurance coverage of non-medication modalities for pain (i.e., physical therapy). The Drug Enforcement agency (DEA) has also been monitoring physicians who over-prescribe opioids; however, this has created another problem: the unavailability of opioids that are essential for pain control. Some studies suggest that individuals in pain end up using the cheaper, readily available heroin, especially when their original prescription has been rapidly terminated.[8] Due to the increase in morbidity and mortality related to opioids and other drugs, harm reduction model such as needle exchange, naloxone rescue kit distribution to individuals with addiction or their families, and safe injection sites has been established.[9,10] Continuous evaluation of all these new modalities, including naloxone administration, is needed.

Naloxone rescue kit

Naloxone nasal spray is a rapidly acting opioid antagonist that quickly reverses the effects of opioid intoxication. Drs. Jack Fishman and Joseph Lewenstein initially invented it in 1961 to treat opioid-related constipation. However, it was later found to be effective in reversing opioid overdose and was approved in 1971 by the Food and Drug Administration (FDA) for parenteral administration.[11] In 2015, the nasal spray formulation was approved as a quick and easily accessible means of administration, especially in non-hospital settings.[11] Some states recently approved and promoted the distribution of this medication to individuals struggling with addiction, their families, law enforcement and emergency medical personal (EMS). The efficacy of naloxone in reversing opioid-related mortality was shown in two major studies. In San Francisco, a recent collaboration between the Department of Public Health and the Drug Overdose Prevention and Education project (DOPE) reported 89% successful reversal of opioid overdose, through training drug users and their families in naloxone administration.[9] A reversal of 399 overdose instances using naloxone was reported. Similar success was also reported in Massachusetts where 327 cases were reversed using naloxone.[12] In a systematic review of published data on naloxone and the implementation of community programs, successful reversal of opioid overdose was reported ranging from 83% to 100%. Where survival rates were low, this was attributed to co-administered drugs of abuse.[13] Additionally, most of the included studies suggested increase in knowledge related to drug overdose among users, with good retention of information. Taken collectively, these studies suggest a significant impact of naloxone on the reversal of mortality related to opioids and accidental overdose.

Risks associated with naloxone administration

Naloxone, although showing distinct positive effects, is not without complications. Side effects from sudden opioid reversal include confusion, reported in 32% of 726 individuals, headaches (22%), nausea and vomiting (9%), aggressiveness (8%), tachycardia (6%), shivering (5%), and seizures (4%).[14] Rarely, death from naloxone has also been reported.[15]

Study rationale

Some studies have questioned whether naloxone administration, without subsequent drug rehabilitation treatment, leads to increased mortality because of continuing addiction and future accidental overdoses. Most of these studies do not report a correlation.[16] However, these studies assessed deaths within 12 hours of naloxone administration. Thus, information on the long-term effect of naloxone reversal and the potential liability to increase the future level of drug consumption due to a false perception of safety is lacking. Although naloxone administration has clearly saved lives in previous studies, our observation of a gradual escalation of accidental drug overdoses in Camden NJ and at the Cooper University Hospital prompted us to investigate the potential of a possible link between opioid-related mortality and naloxone administration. A comparison between less affluent and more affluent communities could help to understand the link, if it exists. Since naloxone was approved for administration by emergency personel by law enforcement personel and even by families in the state of NJ in 2014, analysis of opioid-related mortality, the study was planned to compare opioid mortality rates during 2010-2013 versus those during 2014-2015 in two communities, one affluent (Gloucester), one disadvantaged (Camden).

Hypothesis

As previous studies suggested a decrease in mortality in areas utilizing naloxone to counteract accidental opioid overdose, our hypothesis was a dramatic decrease in mortality after the state approval of naloxone. In April 2014, the state of NJ approved the naloxone distribution to law enforcement, emergency medical personal and families of individuals addicted to opioid. Thus, analysis of mortality in the pre-approval period versus post-approval can yield some insight about the efficiency of this modality option.

Ethics approval

Mortality data was obtained from department of health and since this data included deceased individuals, institutional review board (IRB) approval from Cooper Medical School of Rowan University was not required. The naloxone administration data was obtained from department of health as aggregated analyzed data and thus IRB approval was not required.

Results

Mortality rates showed an increase every year between 2010 and 2015, except for a dip in 2014 (Figure 1) (Table 1).[6,17] According to the US census bureau, Camden county population was 513,657 in 2010, decreasing by 0.7% to 510,150 in 2016. Gloucester county shows similar longitudinal mortality data, and a slight increase (1.4%) in the census from 288,288 in 2010 to 292,330 in 2016. A comparative analysis between naloxone approval and administration by both EMS and law enforcement shows naloxone administration in 2014 by EMS and law enforcement in Camden County shows that it was administered to 208, individuals in 2014 and to 1504 (more than 7-fold increase) in 2015 (Figure 2).

To better understand the other possible differential death rate among the years 2014 versus 2015, analysis of other more potent types of opioids were conducted (i.e., the presence of fentanyl and carfentanyl in the deceased population). Analysis of our data showed the number of fentanyl-related deaths was three in each of the years

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2010 and 2011 in Camden county. The following two years, 2012 and 2013, each had one death related to fentanyl use. However in 2014, the drug-related death rate that was associated with fentanyl use increased to 12 in 2014 and to 54 in 2015 (Figure 3).

Table 1 Drug related mortality rates in Camden and Gloucester County, NJ between 2010 and 2015

Comparison of mortality in two countries						
Mortality/ county	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Camden	89	129	140	158	138	191
Gloucester	40	50	57	71	51	65

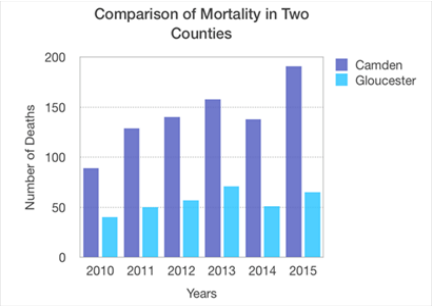

Figure 1 Drug related mortality rates in Camden and Gloucester County, NJ between 2010 and 2015.

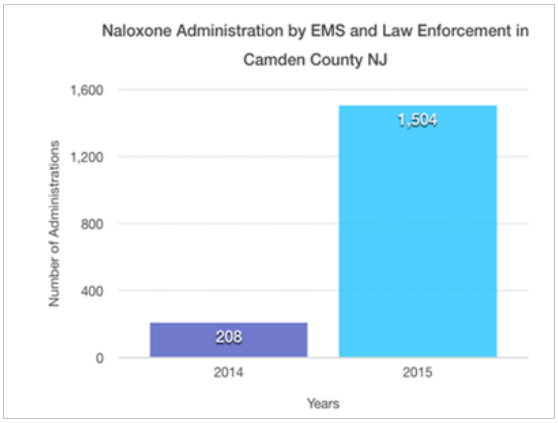

Figure 2 Naloxone administration in Camden County in 2014 and 2015.

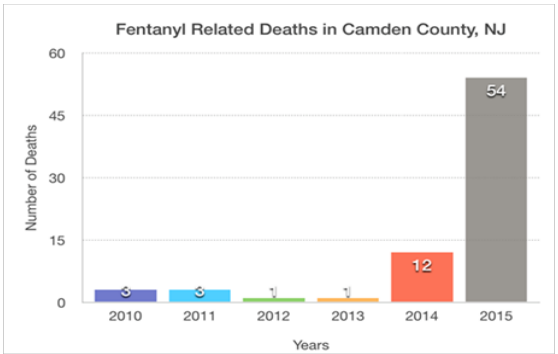

Figure 3 Fentanyl related mortality in Camden County, NJ between 2010 and 2015.

Discussion

In 2014 - 2015, the death rate from synthetic opioids (including fentanyl) increased by 72.2%. This increase is particularly prevalent in Camden county, NJ and more specifically Camden City. It is important to note that the decrease in substance-related death in 2014 (in both Camden and Gloucester Counties) coincided with the state's approval and active distribution of naloxone (April 2014). Despite naloxone's expected efficacy in mortality reduction, a dramatic increase in death rate was later noticed in the year 2015, to a level higher than it was prior to the use of naloxone. This phenomenon is apparent in both in Camden County and Gloucester. There are two potential reasons: first, the availability of naloxone might have created a false sense of security in individuals with substance misuse disorder and thus increased willingness to use more potent substances. Similar phenomena have been documented in other risky health behaviors. In a multi-center cohort study, as an analogy, Surkan et al.[18] demonstrated that the increased knowledge of the availability of combination antiretroviral therapy (cART) for Human Immuno-deficiency virus (HIV) is associated with increased risky sexual behavior in men who have sex with men.[18] Considering the physiological effects of addiction and tolerance and the increasing knowledge of the availability of naloxone and its effectiveness, it makes sense that risk behavior would increase under conditions of greater safety. In a recent study conducted in Boston on 12,192 naloxone recipients after accidental overdose between July 2013 and December 2015, 9.9% of individuals died within the first year, half within the first month.[19] Second, it is known that addicts are constantly chasing the experience that they had with their first consumption of the intoxicating substance in the face of increasing pharmacological tolerance.[20] This means that addicts attempt to increase the amount of a substance in the hope of re-experiencing their first and most exhilarating high.

The other potential reason for the rebound in mortality might be the emergence of potent synthetic opioids among illicit street supplies, particularly fentanyl and carfentanyl. Fentanyl is an opioid analgesic with 50-100 times the potency of morphine.[3] This makes it far too potent for the current 4 mg dose of naloxone to effectively reverse the overdose. The Center for Disease Control (CDC) reported a national increase in the number of fentanyl confiscations in 2014, with the state of New Jersey being the 5th highest with confiscation state (n=238). Considering the increase in opioid potency (i.e., fentanyl and carfentanyl), the FDA suggests a need for naloxone dosage increase in reversing the overdose effects (i.e., a recommendation to increase the number and/or dosage of naloxone nasal sprays being distributed to law enforcement and first responders).[10] In recognition of the significant contribution of fentanyl to drug-related mortality rate, the (DEA) has recently announced the scheduling of all fentanyl-related analogues with the hope of curbing trafficking and distribution.[21]

It is clear that drug-related mortality is on an upward trajectory. Though naloxone has proven effective in reversing the immediate effects of opioid overdose, the increase in risky behavior and the increase in the availability of more potent forms of opioid puts a significant proportion of our population at risk of overdose-related death. Additionally, the association of opioid addiction with concomitant debilitating medical conditions presents an economic concern to Camden, a city that is already stricken by poverty and limited resources.

This study has several limitations. For example, this analysis was conducted in two counties in NJ and, thus, it might not apply

to other geographic areas. In addition, Camden has a predominantly Hispanic and African American population, with more Caucasians in the suburban areas; thus, ethnicity might contribute and change the outcome, although our results showed parallel increases and decreases between Camden and Gloucester. Variables other than naloxone may account for the transient decrease in mortality in 2014 and other than fentanyl and a misperception of safety to the subsequent increase in 2015. Important individual variables such as previous psychiatric and medical diagnoses, finances, employment, as well as family and housing support have not been examined. It is possible that naloxone availability to family members and pharmacists (not examined here) may have changed the findings.

Conclusion

This study concurs with the potential of naloxone rescue kits to save lives. However, it raises the fear that a false perception of safety may increase risk-taking. This is highlighted by the significant decrease in mortality in two New Jersey communities in the year 2014 (the first year of naloxone use) followed by a subsequent increase in 2015. More research is needed to clearly delineate the long-term effects of naloxone programs. According to the results of this study, naloxone alone is not sufficient in combating drug-associated mortality.

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a. AJA: Analyzed the data, wrote the manuscript and finalized it.

b. AA: Analyzed the data, wrote the manuscript and finalized it.

c. KS: Reviewed the analysis, organized the manuscript and finalized it.

d. AP: Reviewed the analysis, organized the manuscript and finalized it.

e. IE: Reviewed and edited the manuscript.

All authors read and approved of the manuscript.

Conflict of interest

All authors declared that they have no competing interest.

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