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Incorporation of Poison Center Services in a State-Wide Overdose Education and Naloxone Distribution Program

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Background: To help curb the opioid overdose epidemic, many states are implementing overdose education and naloxone distribution (OEND) programs. Few evaluations of these programs exist. Maryland's OEND program incorporated the services of the poison center. It asked bystanders to call the poison center within 2 hours of administration of naloxone. Bystanders included law enforcement (LE).
Objective: Description of the initial experience with this unique OEND program component.
Methods: Retrospective case series of all cases of bystander-administered naloxone reported to the Maryland Poison Center over 16 months. Cases were followed to final outcome, for example, hospital discharge or death. Indications for naloxone included suspected opioid exposure and unresponsiveness, respiratory depression, or cyanosis. Naloxone response was defined as person's ability to breathe, talk, or walk within minutes of administration.
Results: Seventy-eight cases of bystander-administered naloxone were reported. Positive response to naloxone was observed in 75.6% of overall cases. Response rates were 86.1% and 70.9% for suspected exposures to heroin and prescription opioids, respectively. Two individuals failed to respond to naloxone and died.
Discussion: Naloxone response rates were higher and admission to the intensive care unit rates were lower in heroin overdoses than prescription opioid overdoses.
Conclusions: This retrospective case series of 78 cases of bystander-administered naloxone reports a 75.6% overall rate of reversal.
Scientific Significance: The findings of this study may be more generalizable. Incorporation of poison center services facilitated the capture of more timely data not usually available to OEND programs. (Am J Addict 2016;25:301–306)

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INTRODUCTION

In an effort to curb the epidemic of opioid overdoses, state, and local health departments have implemented Overdose Education and Naloxone Distribution (OEND) programs.[1–5] Prevention, recognition, and rescue response to opioid overdoses are key components of OEND programs. Training on the rescue response typically includes emphasizing the importance of contacting emergency medical services (EMS), rescue breathing techniques, and administration of naloxone, an opioid antagonist medication currently available via prescription in the United States. Syringe exchange/distribution programs were early adopters of OEND, but recent changes to state laws have allowed for expansion of these programs in order to reach more individuals such as law enforcement (LE), family member, friends, and others.[6–8]

While implementation is an important focus of OEND evaluation, most OEND studies rely on number of people trained, or number of naloxone kits distributed as measures of effectiveness. Others rely on self-reported outcomes and brief questionnaires in convenience samples.[9] As a result, most OEND studies are limited by selection and recall bias, and are not easily generalizable.[10–22]

Implementation of a state-wide OEND program in Maryland incorporated the poison center's 24-hour telephone services for naloxone administration reports. During the OEND training, participants were encouraged to call the poison center within 2 hours of naloxone administration. This poison center intervention enabled real time collection of data related to the administration of naloxone and facilitated tracking of hospitalizations and medical outcomes of overdosed individuals who were transported to the emergency department (ED). This study

describes the first 16 months of this novel component of the OEND program in Maryland.

METHODS

Retrospective analysis of cases reported to the Maryland Poison Center (MPC) from May 1st, 2014 to August 31st, 2015 (16 months) was conducted. During this period, local health departments and private entities across the state gradually implemented the OEND program, and trained bystanders. Bystanders were defined as anyone who was in a position to help an overdose victim and was not a healthcare provider or EMS. Bystanders included LE, family, friends, and acquaintances of overdose victims. The program used the same curriculum for training all bystanders, except that LE were exclusively trained to use intranasal naloxone.

Specialists in poison information (SPIs), nurses, and pharmacists with expertise and certification in assessment and management of poisonings and exposures, staff the poison center. SPIs are available immediately, free of charge to callers, 24 hours per day. For the OEND program, SPIs received education on third party prescribing laws, training entities, dose and route of administration of naloxone, and adverse events of interest. After program implementation, SPIs answered calls and collected data on persons who received bystander-administered naloxone. Callers were LE, family, friends, and acquaintances of the overdose victims; callers also included ED nurses who reported bystander administration of naloxone in an existing ED patient. SPIs conducted additional telephone follow-up if the patient was hospitalized. Follow-up telephone calls ended when the patient was discharged or died. For the study, inclusion criteria were all cases electronically coded as naloxone administered by a bystander.

Data elements included demographics, details on the administration of and response to naloxone, transportation to hospital and hospital course, and post-mortem investigation if applicable. Data on race and ethnicity were not captured, as they are not required by the online data collection system used by poison centers. The AAPCC National Poison Data System (NPDS) manual defines exposure as contact with a drug by any route and for any reason. A subset of routes of exposures was used: ingestion, injection, dermal, or smoking. A subset of reasons for exposure was used: *abuse* as "likely attempting to gain a high, euphoric effect or some other psychotropic effect"; *suicide* as "self-harm or self-destructive"; or *unknown*. Substance identification was by initial narrative and extra narrative obtained during ED stay or hospitalization. Additional substances were based on additional history or laboratory tests (for ethanol). Priority or rank of each substance was by relative contribution to the patient's clinical condition, as per NPDS manual.[23] If the primary substance was not identified as heroin by the narratives obtained in the field, in the ED, or in the intensive care unit (ICU), and there was no evidence of parenteral route of administration, it was classified as "opioid-not specified." "Opioid-not specified" exposures were grouped with exposures to prescription opioids in the analysis. Response to naloxone was positive, if the person was able to breathe, speak, or walk within minutes of administration; *no response* if no change; *unknown response* if unable to determine. Naloxone-precipitated withdrawal was defined as vomiting or agitation observed within minutes of naloxone administration. Causes of death were determined by the Office of the Chief Medical Examiner following autopsies and post-mortem toxicologic investigations.

De-identified data were collected in Microsoft excel 2010. Categorical data were summarized by frequencies and quantitative data by medians and ranges. The University of Maryland's Institutional Review Board deemed the study exempt.

RESULTS

Seventy-eight cases of bystander-administered naloxone met inclusion criteria. There were 43 individuals exposed to heroin, 31 exposed to prescription opioids, and four suspected opioid overdoses that were determined to be non-opioid medical emergencies: one hematologic emergency with neurologic complications, one intracranial hemorrhage, one exposure to synthetic cannabinoids, and one attempted suicide by ingestion of four non-opioid prescription medications. The median age of all cases was 32 years (range 16–68 years; three were unknown adult age) and 59% were males.

Most cases of bystander-administered naloxone, 61/78 (78.2%), occurred in the home; 10/78 (12.8%) occurred in a public setting such as public restrooms or gas stations; 4/78 (5.1%) occurred in a car; one occurred in each of the following: homeless shelter, recovery house, and high school. The vast majority of individuals, 69/78 (88.5%), received naloxone by LE, 9/78 (11.5%) received naloxone by non-LE bystanders (one of which was an off-duty LE officer). The most commonly reported days of the week among the 78 cases were: Saturday (16, 20.5%), Friday (13, 16.7%), Thursday (12, 15.4%), Tuesday (12, 15.4%), Wednesday (10, 12.8%), Sunday (9, 11.5%), and Monday (6, 7.7%). Time of administration was clearly reported in 30/78 cases: between 4PM and midnight (18/30, 60%), 8AM and 4PM (9/30, 30%), and midnight to 8AM (3/30, 10%). The median time for a caller to contact the poison center was 60 minutes (range 0 minutes–18 days) after naloxone administration. Of the 78 cases, two were exposures to substances other than opioids, and two were non-related medical emergencies. Of the remaining 74 exposures, the reason for exposure was "abuse" in 63 (85.1%), attempted suicide in 3 (4.1%), and unknown in 11 (10.8%) cases. Substances used were identified by narratives and are found in Table 1. Of the 31 suspected exposures to prescription opioids, 11 (35.5%) involved additional substances compared to 5/43 (11.6%) of suspected heroin exposures.

TABLE 1. Reported substances and reasons in exposures and medical emergency cases that received naloxone by bystanders

Number of cases ($n = 76$)	Primary substance	Secondary substances	Reasons for exposure
38	Heroin		Abuse (all 38)
15	Opioid-NS		Abuse (9)
Unknown (6)			
2	Opioid-NS	Benzodiazepine	Abuse (2)
1	Baclofen	Methadone + APAP/DPH	Abuse
1	Fentanyl patch		Abuse
1	Heroin	Alprazolam	Abuse
1	Heroin	Cocaine	Abuse
1	Heroin	ETOH	Abuse
1	Heroin	Fentanyl	Unknown
1	Heroin	Cocaine + ETOH	Abuse
1	Methadone	Alprazolam	Abuse
1	Methadone	Morphine	Abuse
1	Morphine		Suicide attempt
1	Morphine	Amitriptyline	Abuse
1	Morphine	Oxycodone + Diazepam	Abuse
1	Opioid-NS	Clonazepam + Cocaine + THC	Suicide attempt
1	Opioid-NS	Cocaine	Abuse
1	Opioid-NS	Cocaine + ETOH	Abuse
1	Opioid-NS	Cocaine + ETOH	Unknown
1	Opioid-NS	Oxcarbazepine + Insulin	Suicide attempt
1	Oxycodone		Abuse
1	Oxycodone/APAP		Abuse
Non-opioid exposures			
1	Clonazepam	Quetiapine + Lithium + Prazosin	Suicide attempt
1	Synthetic cannabinoids		Abuse
Medical emergencies			
1	Neurologic presentation	Intracranial hemorrhage	
1	Neurologic presentation	TTP	

APAP, acetaminophen; DPH, diphenhydramine; ETOH, ethanol i.e. alcohol; NS, not-specified; THC, tetrahydrocannabinol (marijuana);TTP, Thrombotic Thrombocytopenic Purpura.

The most common reason for administration of naloxone was "unresponsive" in 69 (88.5%) cases, followed by "respiratory depression/respiratory arrest" in five (6.4%) cases, "cardiac arrest" in three (3.8%) cases, and one unknown reason. No bystander administered naloxone solely on the basis of pin point pupils. The median dose of naloxone administered was 2 mg (range .4–4 mg) by intranasal route in 76 (97.4%) cases. Twenty persons (25.6%) received more than one dose of naloxone.

Overall response rate was 59/78 (75.6%). Response rates were 86.1% and 70.9% for individuals with exposures to heroin and prescription opioids, respectively. Figures 1 and 2 show the clinical course in 74 cases by opioid categories; the two exposures to substances other than opioids and two non-related medical emergencies were excluded from these figures. One fatality was caused by intoxication of a combination of heroin and fentanyl; the other, methadone and alprazolam.

In total, 26/78 (33.3%) persons had partly incomplete records. These persons either fled the scene and could not be found and were lost to follow-up (13), refused transportation (9), or left the ED against medical advice (4). Fifty-one patients were seen in the ED, the overall hospital admission rate was 25.4% (13/51), 11 were admitted to the ICU, and two were admitted to the psychiatric unit. ICU admission rates were 16.1% (5/31) in heroin overdose patients and 30.0% (6/20) in the prescription opioid overdose patients. Reason for admission to the ICU: seven were intubated and placed on a ventilator for respiratory support or suspected aspiration pneumonitis, only three of these patients had responded to bystander naloxone; four were placed on naloxone infusions, all four had responded to bystander naloxone. Most of the 11 ICU patients remained in the ICU for 24–48 hours except one heroin overdose patient who died after 18 hours (death was due to heroin/fentanyl intoxication) and another heroin overdose patient with delayed post hypoxic leukoencephalopathy, severe rhabdomyolysis, and renal failure who remained in the ICU for 2 weeks.

Naloxone-precipitated withdrawal occurred in 6/78 (7.7%) cases. Agitation was documented in four cases and vomiting in three. The four patients presenting with non-opioid medical

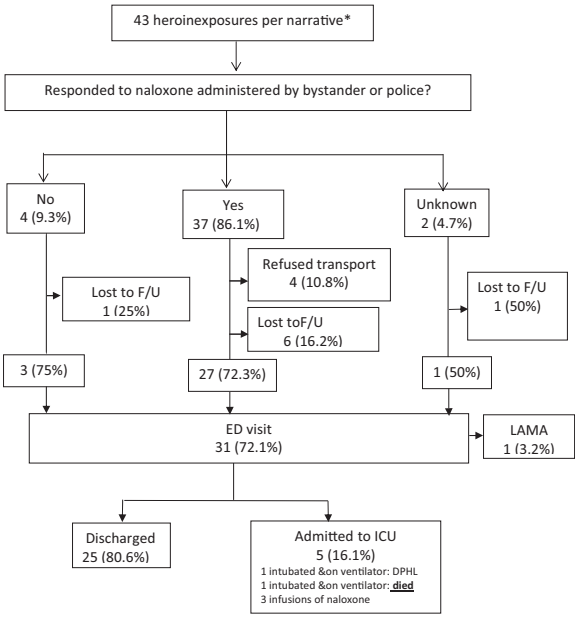

FIGURE 1. Outcomes of bystander-administered naloxone among heroin-exposed individuals. ED, emergency department; Refused transport, refused transportation by ambulance to ED; Lost to follow-up, could not be found; ICU, intensive care unit; LAMA, left against medical advice; DPHL, delayed post hypoxic leukoencephalopathy, *two patients with non-opioid exposures and two patients with medical emergencies were excluded from figure.

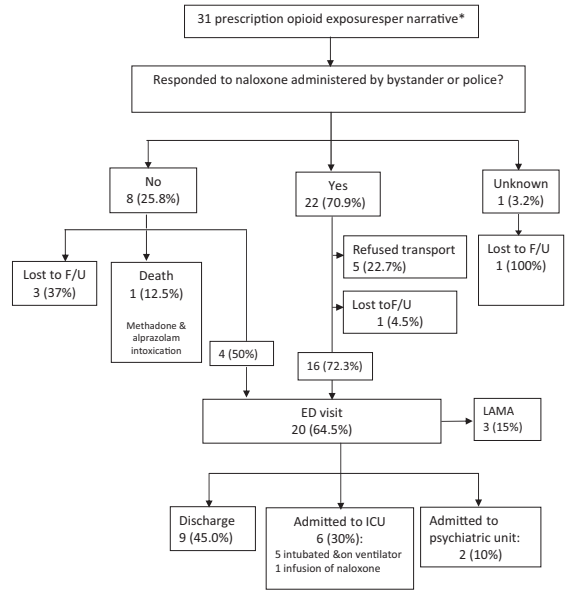

FIGURE 2. Outcomes of bystander-administered naloxone among prescription opioid-exposed individuals. ED, emergency department; ICU, intensive care unit; F/U, follow-up. Lost to F/U includes: refused transport, left against medical advice or could not be found.

emergencies did not experience any adverse events following administration of naloxone.

DISCUSSION

This retrospective case series of a poison center intervention as part of a statewide OEND program provides valuable insight into a unique aspect of this increasingly common approach to curbing the opioid overdose epidemic. Poison center involvement enabled the collection of additional information on the circumstances and outcomes of field-administered naloxone. A key observation is that most of the calls came from LE (89%). This is not surprising given that LE, as a group, represented half those trained in Maryland's OEND program, and LE incorporated "contact the poison center" into their protocols. Most previous OEND research collected information from surveys administered to those presenting to syringe distribution programs requesting naloxone refills. The current study collected data in close to real-time from different settings: injection of heroin; ingestions of prescription opioids; dermal exposures; suicide attempts; and suspected opioid exposures that turned out to not be related to opioid use at all. The findings of this study may be more generalizable because they reflect a wider breadth of exposures.

Overall, 89% of calls to the poison center came within 1 hour of naloxone administration and total call time was short, usually less than 3 minutes. However, some calls were placed days after the incident, contributing heavily to the number of cases lost to follow-up (13/78; 16.6%). The proportion of cases lost to follow-up decreased over the study period, although it resurfaced, and still resurfaces when new training entities join Maryland's OEND program.

The impact of the OEND program on poison center activities was minimal since it utilized existing infrastructure and existing operational procedures. Training of SPIs was simple and quick. In 2015, total exposure call volume to the MPC was approximately 31,000 including over 1,700 opioid exposures (including unintentional pediatric exposures). The additional 78 exposures did not pose an undue burden on poison center activities. Information from the poison center about naloxone administrations was reported to the Department of Health and Mental Hygiene (DHMH) on a weekly basis using automated reporting tools, assisting DHMH in the evaluation of its OEND. Because of automation, the frequency of reports could be easily increased in the future. For example, once the OEND is well-established, daily reports of bystander administration of naloxone could help DHMH in early detection of outbreaks and help coordinate public health responses to LE responses.

Most previous studies of OEND programs have targeted heroin users.[6,12,16,21,22] Few have documented outcomes of bystander-administered naloxone in suspected prescription opioid users. The current study describes the use of naloxone in both types of exposures. Contrary to some current literature, few co-exposures to cardiotoxic medications (beta-blockers,

calcium channel blockers) were observed.[24,25] However, co-exposures to other CNS depressants and cocaine were common (Table 1). Table 1 also includes two "opioid mimics": one exposure to synthetic cannabinoids and one exposure to clonazepam, and quetiapine. The overall response rate to bystander-administered naloxone was 75.6%, with a response rate among heroin-exposed persons of 86%, comparable to that reported elsewhere.[12,19,21] The response rate among prescription opioid-exposed individuals was lower, 71%, potentially because of more mixed substance use. That these response rates were not higher may be due to the following: more stringent criteria for determination of a positive response to naloxone, some previous studies used vague definitions with no time frame as measures of positive responses; illicit fentanyl complicating the overdose; and medical emergencies not related to opioid use.[11] Rates may change in the future as more data are available and new intranasal naloxone products with higher doses and higher concentrations are introduced.

Two patients were exposed to fentanyl. One injected a heroin/fentanyl mix and failed to respond to naloxone. This patient was pronounced dead 18 hours later in the ICU. The other was a patient who applied a fentanyl patch to the skin in order to "get high" and responded to 2 mg of naloxone administered by LE. The patient was transported to the ED where the dermal patch was removed, the skin was decontaminated, and the patient was treated and released after a period of observation.

The ICU admission rate was higher among prescription opioid users (30%) than among heroin users (16%). Reasons for ICU admissions were twofold: need for intubation and ventilation or need for prolonged naloxone infusion. The difference in hospitalization rates is likely due to the different routes of exposures and the different substances ingested. Ingestions result in delayed peak serum concentrations and delays in elimination, ultimately resulting in prolongation of the intoxication. Ingestions of modified-release preparations (eg, OxyContin®, MSContin®), of opioids with prolonged durations of action (eg, methadone), or ingestions of mixed substances can all prolong the intoxication.

Naloxone was re-administered in 25.6% of cases. These data are consistent with other studies of intranasal naloxone and support the practice of distributing more than one dose of naloxone, as well as emphasis on the need to call 911.[20,26,27] Rates of naloxone-precipitated withdrawal were lower than previously reported in the literature.[11,28,29] Rates may change as new formulations of naloxone are introduced.

LIMITATIONS

This study has several limitations. Many bystander naloxone administrations were not reported to the poison center and there was no active systematic method for following all OEND trainees. Delays in calling the poison center resulted in large number of cases that were lost to follow-up. Both of these limitations introduce selection bias that could affect the generalizability of the results.[30] The large number of cases lost to follow-up could also have produced lower adverse events rates. Challenges were encountered in convincing bystanders to call and report to the poison center. Reports of substances relied on the narratives, with no confirmatory urine toxicology screening tests. Also, many urine toxicology screening tests do not assay for synthetic opioids such as fentanyl.

CONCLUSION

This retrospective case series of 78 cases of bystander-administered naloxone reports a 75.6% overall rate of reversal and a low rate of naloxone-precipitated withdrawal. Naloxone is effective and safe in this setting. It is feasible, helpful, and effective to incorporate the existing services of a poison center within a broad OEND program in order to enhance the program, help with clinical assessment, and obtain additional follow up information. This analysis can serve as a guide to inform and support the implementation of such components into OEND programs elsewhere.

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