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POSITION STATEMENT

Expanding Access to Naloxone in the United States

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Background

Drug overdose deaths have increased steadily in the USA since 1979. During the past three decades, drug overdose deaths have tripled [1, 2]. In 2008, the number of unintentional poisoning deaths exceeded the number of motor vehicle deaths for the first time [1]. Of the 38,329 drug overdose deaths in the USA in 2010, 22,134 (60 %) were related to pharmaceuticals, with 75 % of those deaths involving prescription opioid analgesics [3]. Concomitantly, heroin deaths have risen 55 % between 2000 and 2010 [4]. Deaths from use of fentanyl- or acetyl fentanyl-laced heroin were reported in multiple states in 2013 [5–7]. In 2012, the Centers for Disease Control characterized opioid overdose deaths as an epidemic [8]. Most of these deaths are preventable.

In overdose, opioids, including morphine, oxycodone, hydrocodone, methadone, and fentanyl, cause respiratory depression that can lead to hypoxia and, if untreated, death. The exact neuronal mechanisms by which opioids depress respiration in humans are complex. Opioids reduce the sensitivity of the medullary chemoreceptors to hypercapnia [9]. In addition, opioids depress the ventilatory response to hypoxia [10]. The combined losses of hypercarbic and hypoxic drives deprive the victim of the stimulus to breathe. This results in a disruption of the respiratory pattern with prolongation of inspiration and, at higher doses, reduction of chest wall compliance, decrease in tidal volume, slowing of respiratory rate, and apnea [11].

Naloxone is a medication that displaces the opioid agonist from the mu receptor. Timely administration of naloxone reverses opioid-induced respiratory depression, that is, its primary clinical indication. Naloxone is very effective and inexpensive and has been used since 1970 in hospitals and by emergency medical systems (EMS) for this purpose. The Food and Drug Administration (FDA) has approved the intravenous, intramuscular, and subcutaneous routes of administration of naloxone for opioid reversal; onset of action is rapid via any of these routes. While not specifically FDA-approved for intranasal administration, multiple scientific studies support this route of administration. Intranasal administration has been routinely used in many pediatric emergency departments for years [12, 13]. Currently in the USA, naloxone is principally administered in the health-care setting, but use by laypersons is becoming more common.

Most naloxone administered by laypersons is prescribed and distributed as part of ‘overdose education and naloxone distribution’ or ‘bystander naloxone training’ programs, although these programs may have other descriptors. The word bystander is used to identify the family member, friend, or stranger who is in close proximity to the victim at the time of the overdose and specifically not a trained health-care provider. Programs usually include the following key elements:

1. Identify opioids licit and illicit, and non-opioids
2. Recognize a patient with an opioid overdose (vs opioid use)
3. Attempt to rouse and stimulate victim
4. Call 911
5. Rescue breathing
6. Administer naloxone intramuscularly or intranasally

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7. Place victim in left lateral decubitus position while awaiting for 911 to arrive
8. Aftercare (definitive prehospital and hospital medical care for the overdose and its complications) [14–16].

One statewide program involved its regional poison center to help with training, provide telephone assistance to bystanders, and provide surveillance.

Data on the outcomes of bystander overdose training are few. One Australian study observed a decrease in hospitalization rates from 17.7 to 13.9 % ($p<0.05$) in heroin overdose victims who received bystander cardiopulmonary resuscitation but no naloxone prior to ambulance arrival vs those who received neither, supporting the position that training in cardiopulmonary resuscitation reduces harm [17]. Another study found no differences in reversal rates (97 vs 96 %), calls to 911 (23 vs 27 %), and aftercare (89 vs 89 %) in victims who received intranasal naloxone by trained vs untrained bystanders, supporting the position that administration of naloxone reduces harm [18]. It is important to note that there was a very high rate of aftercare in this study and that training of rescuers did not alter the outcome. Although this study does not provide evidence of benefit of training bystanders in the use of naloxone, we believe in this approach until more evidence is available.

Needle exchange/distribution programs were early adopters of naloxone training and distribution, but are no longer the sole model [2]. In a 2010 survey, 188 local programs that distributed naloxone were identified in 15 states and the District of Columbia. The current reach of those programs was somewhat limited, as few were located in states with high overdose fatality rates [2]. Equally limited are systematic evaluations of these programs, reporting tools and evaluations of outcomes. In the span of 14 years, it is estimated that these programs collectively distributed naloxone to over 53,000 persons in the USA and that 10,171 overdoses were reversed [2]. However, it is important to note that most programs measure impact using self-reporting or questionnaires that suffer from selection and information bias [2]. For example, in the aforementioned study, it is not known what proportion of patients defined as having overdosed would have suffered harm without the administration of naloxone or that inappropriate or unnecessary use of naloxone was not labeled as successful reversal.

Administration of naloxone by bystanders is reported in over a dozen feasibility studies with reversal rates ranging from 75 to 100 % of cases [15, 16, 19–30]. Two studies measured the impact of a naloxone program on mortality rates. One study reported a reduction in mortality rates from 46.6 to 29.0 per 100,000 population, but stated that these data were preliminary [30]. The other reported adjusted rate ratios of 0.73 (with a 95 % confidence interval 0.57–0.91) in the implementation group vs the no implementation group [27]. Feasibility studies also report adverse event rates of up to 20 %. Adverse events range from victim's increased annoyance (9–15 %), to precipitation of opioid withdrawal (13–33 %) and possibly seizures (1–4 %) [16, 29]. Life-threatening adverse events such as dysrhythmia and acute respiratory distress syndrome (formerly called non-cardiogenic pulmonary edema or acute lung injury) are rare, only observed in 1–3 % of cases and only after intravenous naloxone were administered, usually by EMS [31–34]. Drawing conclusions regarding safety of bystander naloxone use and true efficacy in saving lives from these studies are limited by many factors such as single case reports, retrospective design, selection bias, and other confounding variables such as preexisting conditions, co-exposures or delays in seeking medical care.

Objections to overdose education and naloxone distribution programs warrant further examination. There are concerns that the relatively short duration of action of naloxone compared to that of some opioids could lead to recurrence of respiratory depression especially if victims refuse transport to the emergency department [35]. Clinical experience supports the effectiveness of single-dose naloxone for short acting opioids. Two studies reported no deaths in the immediate 12 and 48 h following naloxone administration by EMS [36, 37]. Furthermore, many naloxone programs prescribe/distribute two doses, in the event that a single dose is ineffective in the first few minutes. Other objections point to the lack of adequate research on the safety of bystander-administered naloxone and advocate for well-designed experimental trials before widespread adoption. These clinicians argue that opioid users deserve the same high quality, evidence-based practice as other patients [38]. Within the current context of incomplete knowledge and evidence, public health must invoke the precautionary principle: a principle that seeks to implement preventative measures to respond to a real risk in the face of uncertainty regarding a tradeoff between safety concerns, efficacy, and cost issues [39, 40]. The magnitude of the potential benefits to the population (i.e., saving lives) is justification for implementation of an overdose education and naloxone distribution program despite the lack of incontrovertible scientific evidence of benefit or safety [41]. Some suggest that naloxone distribution would result in increased opioid use by giving users a false sense of security and thereby accelerate drug use and its complications. Limited existing survey and observational data do not support this concern. In a survey of heroin injection users, only 6 % (9/142) thought it might increase their heroin use [42]. Two studies observed a decrease in drug use following naloxone distribution. In both instances, the authors attributed the decrease to feelings of empowerment and self-efficiency associated with the training, as neither programs specifically advocated for reduction in drug use, abstinence, or drug treatment [22, 23]. Naloxone precipitates very unpleasant symptoms in individuals with opioid dependence, but not in those who are opioid naïve. Those who have experienced naloxone-induced withdrawal

deny that they feel more comfortable using opioids in higher doses (or with increased frequency) in the presence of naloxone [22]. Specific types of opioids (e.g., heroin, methadone, prescription opioids) and different patient populations (e.g., opioid dependent, polysubstance users) will likely have varying benefit-to-risk relationships for bystander naloxone. These aspects should be individually reported when describing the outcomes of bystander overdose response and naloxone use.

Lastly, while all bystanders are instructed to call 911, it is activated in only 10–60 % of cases [22, 25, 43]. Bystanders reported concerns of police involvement as the major reason for not calling. Fear of outstanding warrants, confiscation of naloxone mistaken as drug paraphernalia by police, drug seizures, fear of eviction, and threat of arrest or incarceration were cited as reasons for not calling 911 [25, 29]. These fears constitute a substantial barrier to care in states where immunity laws for drug-related emergencies are limited or absent [44, 45]. Legal reforms such as Good Samaritan Laws that provide limited immunity from prosecution for bystanders and first responders may help alleviate some of these fears and increase activation of 911. Extending Good Samaritan and indemnification laws to further protect prescribers would also help expand access to naloxone.

Conclusions

ACMT, AACT, and AAPCC recognize the high rates of opioid overdose deaths as a major public health problem. Our organizations support a multi-pronged approach to the treatment of addiction in general and support widening access to naloxone as an opioid safety issue and a harm reduction measure. It is an effective medication whose timely administration will frequently prevent opioid-induced overdose death. Current political and medico-legal barriers excessively restrict access to naloxone for those in need. We recommend the following measures:

1. Expand the mechanisms for low cost and widely available naloxone for bystander administration.
2. Gather additional data regarding effectiveness and safety of bystander-administered naloxone in varying patient populations and regions.
3. Enact laws and regulations that permit the prescribing of naloxone to third parties (bystanders).
4. Enact Good Samaritan Laws that expand access to naloxone and increase the frequency with which bystanders call 911 and access medical care.
5. Educate the population on overdose recognition, recovery positioning, rescue breathing, safe naloxone administration, and aftercare.
6. Encourage the Food and Drug Administration (FDA) along with other regulatory agencies to fast-track approval of naloxone delivery systems that are safe, low cost, and user-friendly.
7. Use the extensive poison center system, which is available 24/7 by a toll-free number (1-800-222-1222), to provide medical advice to bystanders on the use of naloxone, to augment local training, and to assist in collecting data.
8. Support widened access to naloxone beyond hospitals and emergency medical services. This includes, but is not limited to the following:

   (a) Opioid users
   (b) Emergency medical technicians and first responders
   (c) Police officers
   (d) College campus residential assistants
   (e) School nurses
   (f) Substance abuse treatment programs (residential and nonresidential)
   (g) Halfway houses
   (h) Homeless shelters
   (i) Correctional facilities, corrections officers, and soon-to-be-released inmates
   (j) Doctors' offices
   (k) Home visiting nurses
   (l) Nursing homes
   (m) Individuals in close proximity to opioid users

Disclaimer While individual practitioners may differ, these are the positions of the ACMT, AACT, and AAPCC at the time written, after review of the issue and pertinent literature.

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