

# An Innovative Model for Naloxone Use Within an OTP Setting: A Prospective Cohort Study

Joanna G. Katzman, MD, MSPH, Mikiko Y. Takeda, PharmD, MS, Snehal R. Bhatt, MD, Monica Moya Balasch, MS, Nina Greenberg, MS, and Howard Yonas, MD

**Objectives:** Unintentional opioid overdose deaths are a public health crisis, and naloxone is the most effective harm reduction tool to curb many of these deaths. There is growing evidence that take-home naloxone can prevent opioid overdose in targeted populations. The goal of this study is to measure the opioid overdose reversal rate with take-home naloxone among participants with a diagnosis of opioid use disorder (OUD) in an opioid treatment program (OTP) setting.

**Methods:** Patients enrolled in an outpatient OTP program were eligible for this prospective cohort study between April 4, 2016 and July 4, 2016. Two hundred forty-four study participants received overdose education, instruction on how to use naloxone, and were provided with 2 doses of a take-home naloxone auto-injector kit. They were subsequently followed for 3 months.

**Results:** Thirty-one study participants reported overdose reversals using naloxone auto-injector kits on 38 community members. All overdose reversals were heroin-related. Eighty-seven per cent of the community members reversed with naloxone were friends or relatives of the study participants.

**Conclusions:** This study validates that naloxone is not commonly used on the index study participant, but is often used on a secondary

target among people who inject drugs. The large number of overdose reversals reported in this prospective study suggests that this novel model for naloxone use may be replicated at other OTP settings to reduce opioid overdose deaths.

**Key Words:** addiction, harm reduction, naloxone, opioid use disorder, overdose deaths

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Drug overdose deaths have nearly tripled in the past 20 years (Rudd et al., 2016) and are now the leading cause of injury death in the United States (US) (Drug Enforcement Administration, 2015). Over 2 million Americans have an opioid use disorder (OUD) (Hedden et al., 2014), and many who use opioids nonmedically switch from prescription opioids to heroin for multiple reasons, including cost and accessibility (Maxwell, 2015). Currently, the rate of nonmedical use of opioid pain relievers in the US for people aged over 11 years is 4.2%, with higher rates for Hispanics (4.9%) and American Indians (6.9%) (Rieckmann et al., 2012).

The US federal agencies along with addiction and pain societies have issued specific guidelines to educate clinicians and key stakeholders regarding safe opioid-prescribing, the need for medication for addiction treatment (MAT), also known as medication-assisted treatment, which has been widely used to treat OUD with medication (eg, methadone, buprenorphine, naltrexone) and behavioral therapy (eg, counseling) and the use of naloxone as a harm reduction measure to save lives (Kampman and Jarvis, 2015; The White House Office of the Press Secretary, 2015; The Academy of Integrative Pain Management, 2017). The Substance Abuse and Mental Health Administration (SAMSHA) and the Centers for Disease Control (CDC) recently issued recommendations for clinicians to consider co-prescribing naloxone to their high-risk patients with OUD and chronic noncancer pain (Substance Abuse and Mental Health Services Administration, 2013; Hedden et al., 2014; Dowell et al., 2016).

As a pure opioid antagonist, naloxone safely reverses the effects of opioid overdose and has been used for decades to resuscitate patients in hospital settings (Kim and Nelson, 2015). Since 1996, naloxone has been an integral harm reduction tool for community-based overdose education and naloxone distribution programs (Galea et al., 2006). In fact, the epidemic of drug overdoses among people who inject

From the Department of Neurosurgery, School of Medicine, University of New Mexico, 1 University of New Mexico, Albuquerque, NM (JGK); Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico, Albuquerque, NM (MYT); Department of Psychiatry and Behavioral Sciences, University of New Mexico School of Medicine, Albuquerque, NM (SRB); Department of Neurosurgery, School of Medicine, University of New Mexico, Albuquerque, NM (MMB); Department of Mathematics and Statistics, University of New Mexico, Albuquerque, NM (NG); and Department of Neurosurgery, School of Medicine, University of New Mexico, Albuquerque, NM (HY).

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The authors report no conflicts of interest.

Send correspondence to Joanna G. Katzman, MD, MSPH, Professor, Department of Neurosurgery, School of Medicine, University of New Mexico, 1 University of New Mexico, MSC 10-5615, Albuquerque, NM 87131. E-mail: JKatzman@salud.unm.edu.

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drugs (PWID) using heroin is worldwide, and there is growing evidence to support the provision of naloxone to patients with OUD (Darke and Hall, 2003). In the US, opioid overdose is the single greatest cause of mortality among PWID and accounts for more than half of all deaths among people who inject opioids (Latkin et al., 2004).

Many community studies suggest that PWID rarely overdose while alone (Powis et al., 1999; Darke and Hall, 2003) and consistently report a high frequency of witnessing overdose events (Seal et al., 2003; Tracy et al., 2005; Pollini et al., 2006). Moreover, the highest risk for future overdose with PWID seems to be a history of one's own prior overdose (Coffin et al., 2007). PWID also report a reluctance to contact emergency medical services (EMS) upon witnessing an overdose (Seal et al., 2003; Tobin et al., 2005; Tracy et al., 2005; Galea et al., 2006; Strang et al., 2008), and most fatal overdoses occur in private locations such as homes and hotels (Tobin et al., 2005). Qualitative research with PWID indicates that fear of police is a significant barrier to calling EMS during an overdose event (Tracy et al., 2005; Galea et al., 2006). Even when EMS is called to the scene of an opioid overdose, there are significant regional (rural vs urban) differences regarding response times, and overdose reversal outcomes directly correspond to the level of first responder training (Doe-Simkins et al., 2014). Previous community outreach studies with naloxone have shown that opioid overdose education and distribution of naloxone significantly reduces opioid overdose death (Albert et al., 2011; Doe-Simkins et al., 2014).

The primary objective of this prospective cohort study is to measure the number of opioid reversals performed by giving take-home naloxone in this study population. This article is the first large-scale, prospective study to report community benefits of naloxone when provided in an OTP setting.

## METHODS

Between April 4, 2016 and July 4, 2016, 244 study participants at the University of New Mexico's Addiction and Substance Abuse Program (UNMASAP) enrolled in this prospective cohort study. The Addiction and Substance Abuse Program is an OTP which specializes in MAT for adults, adolescents, and pregnant women, and treats approximately 600 patients per year. It is the only clinic in New Mexico with the capacity to provide comprehensive treatment to pregnant women with addictive disorders. The Addiction and Substance Abuse Program also receives referrals for all pregnant women on methadone maintenance treatment throughout New Mexico. Currently, 64% of UNMASAP enrollees on MAT are women and 11% are pregnant. This prospective study provided an opportunity to evaluate use of naloxone in a female dominant study cohort. In addition, approximately 80% of patients had previously used intravenous heroin, whereas 20% of patients had primarily used prescription opioid analgesics before beginning MAT at UNMASAP.

This study was registered in the NIH Clinical Trials NCT02669901 on December 21, 2015, and was approved by the University of New Mexico Human Research and Review Committee (a.k.a. IRB) on March 18, 2016 (study ID: #15-616). All human participants gave written informed consent.

A Certificate of Confidentiality is on record at the NIH for this study. The inclusion criteria of this study were all patients with an OUD; treated with methadone, buprenorphine, or naltrexone as MAT at the UNMASAP; and aged 18 or older. Exclusion criteria were all patients allergic to naloxone and its inactive ingredients (eg, buffering agents); and younger than 18 years.

## Initial Visit

Once the study was approved by the IRB, informational flyers were posted at UNMASAP to inform potential participants. The study coordinator was available during all clinic hours to enroll and educate study participants and their companions (when available) on the signs and symptoms of opioid overdose; appropriate response during an overdose (calling 911, rescue breathing, and remaining with the person until EMS arrives); and how to use the naloxone auto-injector (Kaleo Inc., 2014). Participants in this study were encouraged, but not required, to bring a companion to the initial visit. If the study participant did not bring a companion, he/she was highly encouraged to educate his/her closest friend/relative in how to use naloxone in case of overdose. Companion attendance at the initial visit was recorded.

Naloxone was distributed at the initial visit. The study coordinator spent about 15 to 20 minutes with each participant in a private treatment room at UNMASAP obtaining baseline information which included demographics, social history, medical history, and history of illicit drug use. Education on opioid overdose and rescue breathing was also provided during this time. At the end of the visit, 1 naloxone auto-injector kit (2 naloxone auto-injectors and 1 training auto-injector per kit) was given to each study participant. The research coordinator demonstrated naloxone kit use to the participant until he/she reported self-efficacy and performed proper kit use.

## Follow-up Visit

Every study participant was asked to follow up at 3 months regardless of whether or not their naloxone kit was used. Of 244 participants, 215 participants completed a 3-month follow-up visit and additional visit(s) if/when a naloxone auto-injector replacement kit was needed. At each follow-up/replacement visit, the study coordinator conducted a short interview to ascertain if and why a replacement kit was needed (lost, stolen, or overdose [OD]). If the participant used the kit for opioid overdose, then more detailed information was collected, such as number of naloxone doses used in the event of an OD, details of the clinical outcome of the person overdosing (ie, successful overdose reversal, death, and utilization of healthcare institution [eg, EMS, emergency room, hospitalization]), relationship to the person rescued (family, friend, stranger), causality (ie, type[s] of opioid), and whether or not 911 was called after utilization of the naloxone auto-injector kit. The observation period ended after the enrollee's 3-month follow-up visit.

## Statistical Analysis

Statistical analysis was performed using Stata Version 12 (College Station, TX). The research team (MM, MYT, NG)

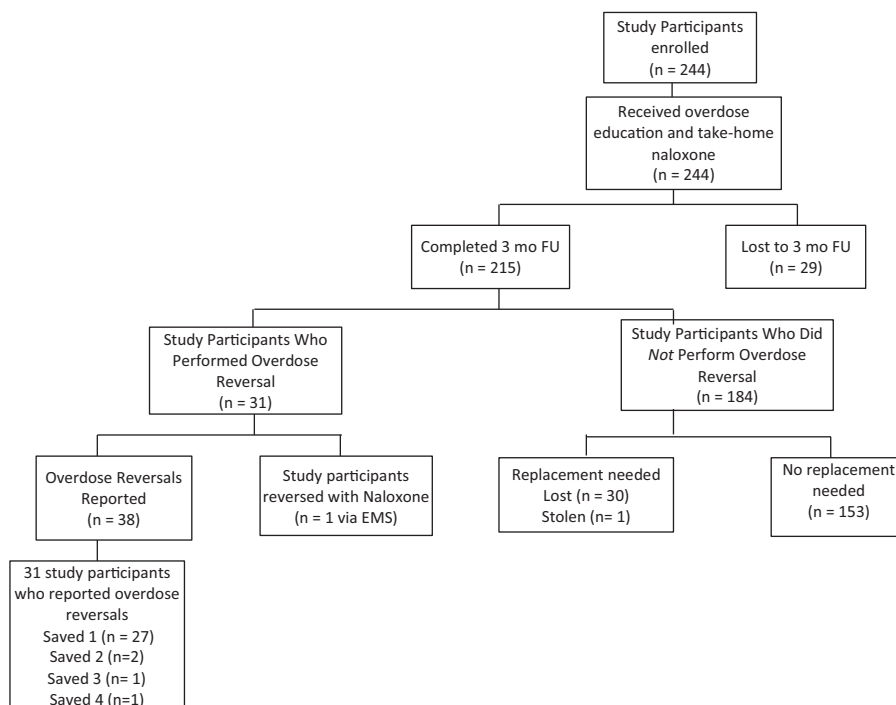


FIGURE 1. Study design and results.

collected the data and used a descriptive analysis for demographic, social status, education, and past overdose history. Significant differences in the UNMASAP and the study population were tested using chi-square analysis.

### RESULTS

Between April 4, 2016 and July 4, 2016, 244 study participants were enrolled into this study. The observation period continued for 3 months for each study participant. During this time, 31 study participants reported overdose reversals using their naloxone auto-injector kits on 38 community members. This demonstrates that 13% of the study participants used the take-home naloxone to perform an overdose reversal in the community. Figure 1 shows the summary of the recruitment status and overdose reports from the participants. All reported overdose reversals were successful, and all involved PWID with heroin. Of these reported overdose reversals, 50% (n = 19) required 1 dose of naloxone, 45% (n = 17) required 2 doses of naloxone, and 5% (n = 2) required 3 doses of naloxone. For the 2 overdose reversals requiring 3 doses of naloxone, the third naloxone dose was delivered by EMS for 1 individual, whereas the second individual received a third dose from a study participant who had an extra naloxone dose available. Among 31 study participants who reported opioid overdose reversals, 21 participants were female (67.7%) and 10 were male (32.3%).

Emergency medical services were called 48% of the time for these 38 reported overdose reversals. Only 1 study participant overdosed during this study period, and she was rescued with naloxone by EMS. This same study participant

also reported using naloxone for an overdose reversal with a community member.

The most common reasons for study participants “lost to follow-up” were relocation and discontinuation with MAT at UNMASAP. Except for the patients who were discharged

TABLE 1. Demographics and Medication Treatment

Demographics	n	%
Sex		
Female	174	71.3
Male	70	28.7
Race		
Hispanic/White	154	63.1
Non-Hispanic/White	66	27.1
American Indian/Alaska Native	12	4.9
Black or African American	2	0.8
Asian	1	0.4
Not Reported	8	3.3
Unknown	1	0.4
Age		
18–19	4	1.6
20–29	92	37.7
30–39	64	26.2
40–49	30	12.3
50–59	36	14.8
≥60	18	7.4
Medication treatment		
Methadone	193	79.4
Buprenorphine	42	17.3
Naltrexone (oral or intramuscular)	6	2.5
No opioid replacement therapy	3	1.2
Companion attendance		
Present	25	10.3
Not present	219	89.8

from UNMASAP due to behavioral reasons, all study participants “lost to follow-up” were called by the research coordinator on the telephone in an attempt to have them rejoin the study.

### Demographics

Table 1 shows distributions of sex, race, age, opioid replacement therapy, and companion attendance for study participants.

The cohort of 244 study participants included 174 females (71%) and 70 males (29%). There was no statistically significant difference in the UNMASAP clinic sex distribution, which had 65% females and 35% males ( $P = 0.108$ ) on September 2, 2016. The UNMASAP clinic gives priority access to pregnant women and mothers with newborns.

At the initial study intake, 44% ( $n = 108$ ) of the study participants stated that they had personally overdosed at least once in their life, whereas 87% ( $n = 200$ ) had witnessed someone else overdose at least once in their life.

### Type of Medication Treatment

Of the 244 study participants, 80% ( $n = 193$ ) were prescribed methadone, 17% were prescribed buprenorphine ( $n = 42$ ), and 3% ( $n = 6$ ) were prescribed naltrexone, in addition to participating in their regular behavioral therapy programs.

### Overdose Education, Take-home Naloxone, and Reported Overdose Reversals

Ten per cent ( $n = 25$ ) of study participants brought a companion with them to the initial visit of opioid overdose education and take-home naloxone distribution, whereas most study participants (90%,  $n = 219$ ) did not have a companion with them during the initial visit. Four study participants who brought a companion to the overdose education also performed an overdose reversal in the community.

Of the 31 study participants who performed overdose reversals on community members, 27 study participants reported 1 reversal, 2 reported 2 reversals, 1 reported 3 reversals, and 1 reported 4 reversals. Out of the 38 overdose reversals, 87% were known by the study participants (acquaintance, friend, family member, significant other), whereas 13% were strangers to the study participants (Table 2).

## DISCUSSION

### Study Participants as Bystanders

All study participants were trained in drug overdose recognition and in use of the naloxone auto-injector. The

initial intake took approximately 15 to 20 minutes, which is consistent with the minimal training needed in other studies (Behar et al., 2015; Takeda et al., 2016). Only 10% of study participants brought a close family member or friend to the initial visit for naloxone training. This small percentage of companions present during the initial visit was not unexpected since most patients travel alone to UNMASAP for their regular visits. The 1 study participant who experienced an overdose did not have a companion at her initial visit and was rescued by EMS. Each of the 31 study participants (including the 1 study participant who overdosed herself) acted in the capacity of a “bystander” as they performed overdose reversals on 38 community members. A bystander is a person who may have received training on identifying opioid overdose, but is able to perform rescue breathing and can administer naloxone (Walley et al., 2013). In this study, 21 of 31 participants reporting reversals were females, which closely resembles the percentage of female study participants enrolled. This study demonstrates that females are quite capable of acting as a bystander and performing overdose reversals with naloxone.

These results are consistent with existing literature demonstrating that people with OUD are willing to administer naloxone during an overdose if the medication is made directly available to them (Seal et al., 2003; Galea et al., 2006; Strang et al., 2008; Clark et al., 2014). This validates the concept that the recipient of naloxone is usually not the patient for whom the naloxone has been given or prescribed. Instead, the naloxone is most often used on someone else. Training of the patient who is given naloxone builds the capacity to respond in a timely and effective manner to reverse overdose in another individual (Strang et al., 2008).

The rate of overdose reversal in this study population was high and may relate to study participants acting as bystanders for community members at high risk for opioid overdose. For every 100 study participants enrolled, approximately 16 overdose reversals were performed on community members by the enrollees themselves. Our data confirm that a high percentage of participants in this study have either witnessed (87%) an overdose event or have been rescued (44%) by naloxone previously. Naloxone is used frequently by those who inject heroin, and this familiarity can increase the chance for overdose reversals performed (Sherman et al., 2007; Des Jarlais et al., 2009). Perhaps, the study participants in our cohort who have acted as a bystander and performed overdose reversal(s) are unique in their capacity to help others. It is possible that these individuals can eventually serve a role in the community as peer educators.

### Should Mandatory Take-home Naloxone Distribution be Required in Federally Qualified Opioid Treatment Programs (OTPs)?

Although the SAMSHA opioid tool kit suggests prescribing naloxone to patients who have a history of opioid substance use disorder, this remains a recommendation to providers and patients, and not a requirement (Substance Abuse and Mental Health Services Administration, 2013). The recent CDC guidelines, published for pain management,

**TABLE 2.** Relationship of Study Participant Who Performed Overdose Reversal on Community Member

Relationship to Study Participant	n	%
Acquaintance	4	10.5
Family member	6	15.8
Friend	20	57.9
Significant others	3	2.6
Stranger	5	13.2

also suggest, but do not require, co-prescribing naloxone for those patients with a substance use disorder, history of overdose or taking a high opioid dosage, which they specify as 50 morphine milligram equivalents per day (Dowell et al., 2016). Patients treated in methadone maintenance treatment centers during the induction period remain at high risk for opioid overdose (Kimber et al., 2015).

We have also seen in our study that the participants perform opioid overdose reversal(s) in their community quite readily. Historical medication data from UNMASAP has revealed that less than 10% of our cohort was prescribed naloxone during the 2 years before study enrollment. It is the authors' contention that take-home naloxone combined with opioid overdose education is critically important to continuing the success of the overdose reversals performed in this environment. A written prescription for naloxone may not have the same impact.

### Limitations

Because of the Health Insurance Portability and Accountability Act, direct outcome assessment of the community members who were treated with naloxone for an overdose reversal was not possible. It is impossible to know which community members would have survived without the naloxone provided to them. Many people survive overdose from heroin and prescription opioid pain relievers without naloxone or EMS support.

### CONCLUSIONS

This prospective study demonstrates that there are a significant number of overdose reversals reported in the community by study participants in an OTP setting who received opioid overdose education and were given take-home naloxone. In this study, naloxone is not commonly used on the index study participant, but is most often used on a secondary target among PWID. It appears that social contacts are a critical harm reduction component to the overdose reversals seen within the community associated with PWID. It is the authors' contention that take-home naloxone should be considered a necessary component of any federally qualified OTP program. The authors anticipate that future naloxone investigation may focus on the identification of specific characteristics of study participants performing overdose reversals compared with the study participants who did not use the naloxone. Additionally, the authors hope to perform qualitative ethnographic interviews on study participants who did and did not perform overdose reversal(s) in the community.

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