



## Naloxone Distribution and Cardiopulmonary Resuscitation Training for Injection Drug Users to Prevent Heroin Overdose Death: A Pilot Intervention Study

EXHIBIT

Hochhaus 2 (4-14-2020)

exhibitsticker.com

Karen H. Seal, Robert Thawley, Lauren Gee,  
Joshua Bamberger, Alex H. Kral, Dan Ciccarone,  
Moher Downing, and Brian R. Edlin

**ABSTRACT** *Fatal heroin overdose has become a leading cause of death among injection drug users (IDUs). Several recent feasibility studies have concluded that naloxone distribution programs for heroin injectors should be implemented to decrease heroin overdose deaths, but there have been no prospective trials of such programs in North America. This pilot study was undertaken to investigate the safety and feasibility of training injection drug using partners to perform cardiopulmonary resuscitation (CPR) and administer naloxone in the event of heroin overdose. During May and June 2001, 24 IDUs (12 pairs of injection partners) were recruited from street settings in San Francisco. Participants took part in 8-hour training in heroin overdose prevention, CPR, and the use of naloxone. Following the intervention, participants were prospectively followed for 6 months to determine the number and outcomes of witnessed heroin overdoses, outcomes of participant interventions, and changes in participants' knowledge of overdose and drug use behavior. Study participants witnessed 20 heroin overdose events during 6 months follow-up. They performed CPR in 16 (80%) events, administered naloxone in 15 (75%) and did one or the other in 19 (95%). All overdose victims survived. Knowledge about heroin overdose management increased, whereas heroin use decreased. IDUs can be trained to respond to heroin overdose emergencies by performing CPR and administering naloxone. Future research is needed to evaluate the effectiveness of this peer intervention to prevent fatal heroin overdose.*

**KEYWORDS** *Heroin, Heroin-related deaths, Injection drug use, Overdose, Prevention.*

### INTRODUCTION

Dramatic increases in the incidence of fatal opiate overdose have shadowed burgeoning heroin epidemics in several countries.<sup>1,2</sup> In the United States, each year, more injection drug users (IDUs) die from heroin overdose than from any other cause, including AIDS, hepatitis, or homicide.<sup>3</sup> In fact, heroin overdose was the single

Dr. Seal is with the Department of Medicine, San Francisco VA Medical Center, University of California, San Francisco, California; Mr. Thawley, Ms. Gee, Dr. Kral, Dr. Ciccarone, Mr. Downing, and Dr. Edlin are with The Urban Health Study, University of California, San Francisco, California; Dr. Bamberger is with the San Francisco Department of Public Health, San Francisco, California; and Dr. Edlin is also with the Center for the Study of Hepatitis C, Weill Medical College of Cornell University, New York, New York.

Correspondence: Karen H. Seal, Department of Medicine, San Francisco VA Medical Center, University of California, San Francisco, 4150 Clement Street, Box 111-A1, San Francisco, CA 94121. (E-mail: karens@itsa.ucsf.edu)

largest cause of accidental death in San Francisco, California from 1997 to 2000.<sup>4</sup> Many of these deaths are preventable because heroin overdose can be readily reversed through the timely injection of naloxone, a legal, unscheduled opiate antagonist routinely used by emergency medical personnel to quickly and safely reverse opiate overdose.<sup>5</sup> Peers witness most overdoses,<sup>6</sup> but deaths occur because drug users are hesitant to summon emergency medical services for fear of police involvement<sup>7,8</sup> and their attempts at resuscitation are often unsuccessful.<sup>8,9</sup>

Naloxone effectively reverses opiate overdose. Naloxone precipitates acute withdrawal symptoms in opiate-dependent persons, but has no effect on nonopiate users; serious adverse effects are rare and naloxone has no abuse potential.<sup>9</sup> Several feasibility studies have concluded that if injection heroin users were provided naloxone and resuscitation training, including training in CPR and rescue breathing, they might be able to intervene to prevent heroin overdose fatalities in their peers.<sup>8,10,11</sup> Recently, through both underground and government-sponsored programs, naloxone has been made available to drug users in Germany, Italy,<sup>12,13</sup> and in the United States, in Baltimore, Maryland, Chicago, Illinois<sup>14</sup> and Rio Arriba County, New Mexico.<sup>15</sup> There have been no formal evaluations of these programs however, and thus their effectiveness has not been established.<sup>14,16,17</sup>

Although naloxone is not routinely prescribed to laypersons in the United States, naloxone distribution programs are being planned or considered in the United States—in other localities including New York City, New Haven, Connecticut, and several counties in Northern California. These programs have encountered political barriers, however, owing to concerns that naloxone will be viewed by drug users as a “safety net,” thus enabling more drug use, increasing the number of overdoses, and decreasing the use of emergency services.<sup>18</sup> Moreover, while the legality of prescribing naloxone to laypersons for use in others who overdose has been called into question by politicians and physicians alike, a recent legal analysis provides justification for the prescription of naloxone.<sup>5</sup> To date, there have been no prospective trials of naloxone distribution in North America to investigate these specific concerns. In collaboration with the San Francisco Department of Public Health, the Urban Health Study at the University of California, San Francisco developed and implemented a pilot overdose prevention and management program to train heroin injectors to perform cardiopulmonary resuscitation (CPR) and administer naloxone to injection partners in the event of a heroin overdose emergency. Participants were followed for 6 months to investigate the safety and feasibility of this intervention.

## METHODS

### Study Participants

During May and June 2001, 487 IDUs participating in the Urban Health Study, a semiannual cross-sectional serosurveillance study of injection drug users (IDUs), were recruited from street settings in San Francisco and screened for enrollment. IDUs were eligible if they injected heroin at least twice a week, reported one or more heroin overdoses in the past 5 years, and could enroll together with an eligible injection partner who met the same criteria. The study was approved by the University of California, San Francisco Committee on Human Research, and each participant provided written informed consent.

### **The Overdose Prevention and Management Program**

Twenty-four eligible, consenting IDUs enrolled in the study in pairs and underwent overdose prevention and management training in July and August 2001. The overdose prevention and management program was modeled after existing community-based naloxone distribution programs in Chicago and San Francisco<sup>19</sup> and consisted of four 2-hour interactive training sessions facilitated by experienced counselors. Sessions were held at convenient community-based field sites, and participants were reimbursed for their time at each session. Before beginning the training sessions, study staff met with local police to describe the program and to apprise them that participants would be carrying naloxone and using it in the event of an overdose. Moreover, police were educated about users' reluctance to call 911 for an overdose because of the perception that arrests were made in conjunction with these emergency overdose calls.

In Session 1 of the program, participants acknowledged the impact of heroin overdose on their lives by describing past experiences with heroin overdose including the loss of friends and family. Subsequently, participants were trained to recognize a life-threatening heroin overdose, defined as being unresponsive, with or without cyanosis, and/or as having slowed, shallow or absent respirations. Overdose prevention strategies were reviewed which included not using alcohol or sedatives together with heroin, not injecting alone, and starting with smaller doses after a period of abstinence or when using heroin from an unfamiliar source. Session 2 was hands-on; participants learned to perform rescue breathing and CPR and practiced emergency overdose resuscitation with their injection partners. (Fig. 1)

Accessing emergency medical services (calling 911) after using naloxone for an overdose was the focus of Session 3. Staff reviewed the importance of definitive medical help to manage any complications of the overdose, including the victim's withdrawal symptoms, after receiving naloxone. Participants listed barriers to calling 911 for an overdose including lack of access to a telephone and fear of police arrest. Participants role-played calling 911 in such a way as to elicit a rapid medical response without necessarily triggering police involvement. In Session 4, participants learned to safely and appropriately administer naloxone using the contents of the naloxone kit (see below). Participants were instructed to inject one 0.4 mg dose of naloxone intramuscularly and repeat in 5 minutes if the victim remained unresponsive. Finally, they developed and rehearsed individualized rescue plans to be used by their partner in the event the other overdosed.

### **The Naloxone Kit**

Under the auspices of the San Francisco Department of Public Health, study physicians dispensed a labeled naloxone kit to each participant contingent on successful completion of the training program. Each kit included two 0.4 mg prefilled injection cartridges of naloxone with two injection devices, gloves, a rescue breathing mask, and detailed instructions all packaged inside a plastic case that also contained a safe compartment for used needles (Fitpacks, ASP Harm Reduction Systems, Australia). (Fig. 2) We chose to use 0.4 mg prefilled, single-dose, injection devices to minimize the likelihood of severe opiate withdrawal reactions from larger doses, eliminate the need to draw up the medication during an emergency, assure the availability of a sterile needle and injection device when it was needed, and reduce the likelihood of infectious disease transmission through a nonsterile syringe or multi-dose vial.<sup>20</sup> Participants were given a written prescription for naloxone in case they needed additional evidence that they were carrying a legally prescribed drug.



**FIGURE 1.** Participants practicing naloxone injection with their injection partner during the overdose prevention and management program.

#### **Data Collection and Statistical Methods**

Participants were interviewed monthly for 6 months. Data were collected on overdose-related knowledge, overdoses witnessed or experienced by study participants, and drug and alcohol use. Knowledge was assessed by asking participants to name identifying features of heroin overdose, risk factors for overdose, and overdose prevention and management strategies.

Participants were asked to contact study staff as soon as possible after witnessing or experiencing an overdose. Participants were interviewed in-depth after each overdose they witnessed or experienced, usually within 24–48 hours. Overdose events, including specific details, were confirmed by interviewing one or two witnesses.



**FIGURE 2.** The naloxone kit.

To further verify the overdose event, when possible, records were obtained from San Francisco Emergency Medical Services, local hospital emergency departments, and the medical examiner. We excluded one death reported by a participant because it could not be confirmed by witnesses, paramedics, police, or hospital, or medical examiner records.

Frequencies were calculated for categorical variables and medians with interquartile ranges (IQR) were calculated for continuous variables. Questions testing knowledge of overdose prevention and management were scored, and the scores were dichotomized and compared with baseline using a McNemar's  $Q$  test. Number of overdoses, drug use frequency, and entry into drug treatment were compared at baseline and during 6 months of follow-up by using Wilcoxon signed-rank test for ordinal outcomes and a McNemar's  $Q$  test for dichotomous outcomes.<sup>21</sup>

## RESULTS

Twelve pairs of injection partners ( $n=24$  IDUs) enrolled and all completed the overdose prevention and management program. Of the participants, 33% were female, 46% African American, 54% white and 54% homeless. The median age was 41 years (IQR=34–49 years), and the median duration of injection drug use was 22 years (IQR=11–28 years). There were no statistically significant demographic differences between the 24 participants in the Overdose prevention and management program and the other 463 participants in the Urban Health Study.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.