



Published in final edited form as:

Subst Abus. 2015 ; 36(2): 240–253. doi:10.1080/08897077.2015.1010032.

A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming into Clinical Practice

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Abstract

Background—As physicians have increased opioid prescribing, overdose deaths from pharmaceutical opioids have substantially increased in the United States. Naloxone hydrochloride (naloxone), an opioid antagonist, is the standard of care for treatment of opioid induced respiratory depression. Since 1996, community-based programs have offered overdose prevention education and distributed naloxone for bystander administration to people who use opioids, particularly heroin. There is growing interest in translating overdose education and naloxone distribution (OEND) into conventional medical settings for patients who are prescribed pharmaceutical opioids. For this review, we summarized and classified existing publications on overdose education and naloxone distribution to identify evidence of effectiveness and opportunities for translation into conventional medical settings.

Methods—For this review, we searched English language PubMed for articles on naloxone based on primary data collection from humans, including feasibility studies, program evaluations,

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AUTHOR CONTRIBUTIONS

SR Mueller, IA Binswanger, and AY Walley conceived of the review. SR Mueller, IA Binswanger, AY Walley and JM Glanz formulated the methods for the review. SR Mueller conducted the search of the literature. SR Mueller, IA Binswanger, AY Walley and SL Calcaterra reviewed the articles. All authors interpreted the review findings. SR Mueller drafted the manuscript. All authors reviewed and provided critical revisions to the manuscript. All authors give final approval for publication.

The authors declare that they have no conflicts of interest.

surveys, qualitative studies and studies comparing the effectiveness of different routes of naloxone administration. We also included cost-effectiveness studies.

Results—We identified 41 articles that represented 5 categories: evaluations of OEND programs, effects of OEND programs on experiences and attitudes of participants, willingness of medical providers to prescribe naloxone, comparisons of different routes of naloxone administration, and the cost-effectiveness of naloxone.

Conclusions—Existing research suggests that people who are at risk for overdose and other bystanders are willing and able to be trained to prevent overdoses and administer naloxone. Counseling patients about the risks of opioid overdose and prescribing naloxone is an emerging clinical practice which may reduce fatalities from overdose while enhancing the safe prescribing of opioids.

Keywords

overdose; opioids; prevention; primary care

INTRODUCTION

Unintentional poisoning represents a significant, growing problem in the United States.^{1–5} Drug poisoning fatalities now exceed deaths from motor vehicle crashes.⁶ In 2010, opioid poisonings accounted for over 16,000 deaths.⁷ Unintentional poisoning from pharmaceutical opioids has become an epidemic in the last decade, in part due to increasing opioid analgesic availability.⁸ Overdose education and provision of naloxone is one approach to address this epidemic.

Naloxone is a short-acting opioid antagonist used by medical practitioners to reverse opioid overdose since 1971. In the United States, it is approved by the Food and Drug Administration (FDA) for prescription use.⁹ Naloxone antagonizes opioid effects by displacing opioid agonists from opioid receptors in the central nervous system, reversing respiratory depression. Naloxone can be administered intranasally (IN), intramuscularly (IM), intravenously (IV), or subcutaneously and is effective against all opioid agonists, including morphine, heroin, oxycodone, and methadone. To reverse long-acting opioids, the dose may need to be repeated. The major adverse effect of naloxone in opioid-dependent patients is precipitated opioid withdrawal. This effect results from the rapid displacement of opioid agonist from the opioid receptor, the same mechanism by which naloxone also reverses respiratory depression. Naloxone has no psychoactive properties, is not a scheduled drug, and has no abuse potential.¹⁰

Community-based and public health organizations have developed overdose education and naloxone distribution (OEND) programs to prevent opioid overdose fatalities among people who use heroin, and, more recently, among people who use pharmaceutical opioids. In a survey of OEND programs completed in 2010, 188 programs located in 15 states and the District of Columbia provided take-home naloxone to people who used opioids.¹¹ From 1996 to 2010, these programs had trained and distributed naloxone to over 50,000 persons and received reports of over 10,000 overdose reversals.¹¹ Prevention strategies employed by

these OEND programs may be applicable to the prevention of pharmaceutical opioid overdose deaths in primary care and specialty medical practices.

Provision of naloxone as a part of a strategy to address opioid overdose has been endorsed by several US Federal agencies.¹² In 2013, the Substance Abuse and Mental Health Services Administration released the Opioid Overdose Prevention Toolkit to provide communities and local governments information to develop policies to prevent opioid related deaths.¹³ Scotland and Wales recently developed national naloxone distribution programs.¹⁴ In early 2014, Norway began offering naloxone for the first time in intranasal form.¹⁵ Other countries to allow for the distribution of naloxone include Sweden,¹⁶ England,¹⁷ Germany,¹⁸ Italy,¹⁹ Canada,²⁰ and Australia.²¹

Conventional medical settings, such as primary care, pain clinics, emergency departments, and addiction treatment centers are potential venues for overdose education and naloxone prescription. These sites provide opioid prescriptions or medications and patients may present to these sites with complications from opioid use. Our aim was to review and classify existing publications on OEND and naloxone in community-based settings. We sought to identify evidence of effectiveness and opportunities for translation of these practices into conventional medical settings.

METHODS

Search Strategy and Article Selection

One author searched English language PubMed for peer-reviewed, original research articles through May 2014 using the following Medical Subject Heading (MeSH) terms: *naloxone*, *drug overdose*. This search yielded 254 articles. Two authors reviewed the abstracts of the 254 articles and excluded 221 articles because they were non-human studies, studies that did not focus on pre hospital-based administration of naloxone, efficacy studies in controlled settings, commentaries and perspectives, medical news articles, and policy or legal reviews. Based on the aim of our review to inform OEND programming in conventional medical settings, we included original peer-reviewed articles that involved primary data collection from patients or medical providers about OEND programs, including feasibility studies and program evaluations (if they included data collected from participants), surveys and qualitative studies of attitudes towards take-home naloxone, and studies comparing the effectiveness of different routes of naloxone administration in pre- and non-hospital settings. We also included cost-effectiveness studies. We also consulted national content experts and 3 of the authors searched the reference lists of the included articles, producing 7 additional articles which met inclusion criteria. A final consensus was reached by these 3 authors on the 41 articles included in this review. For reporting purposes, we then classified the articles into 5 major topic areas. A PRISMA diagram (Figure 1) summarizes articles that were included in our initial search and were excluded based on our article selection criteria.²²

Article Abstraction

Two of the authors reviewed each article and recorded the location, the number of participants, the population, the study design, the questions addressed by the article, and a

summary of key findings. Given the early stage of research in this area and the heterogeneous methods and outcomes employed, we chose not to apply systematic methods, such as meta-analysis, to summarize outcomes.

RESULTS

We identified 41 articles that met our inclusion criteria (Table 1). After reviewing articles that met inclusion criteria, we categorized the articles into 5 topical categories. Nineteen articles evaluated overdose prevention programs. These studies were largely observational in nature and included evaluations of programming. They also included 4 prospective cohort studies which followed participants over time.^{18, 23–25} The next set of articles (n=11) evaluated the effects of OEND programs on the experiences and attitudes of participants. These included qualitative (n=4) and survey (n=7) studies. Four articles described willingness of medical providers to prescribe naloxone. Five studies compared routes of naloxone administration in pre-hospital settings. In this category were 4 prospective studies, of which 2 were observed cohorts and 2 were randomized trials. Finally, two studies evaluated the cost-effectiveness of naloxone. The following results summarize our findings.

Evaluation of Overdose Education and Naloxone Distribution Programs

Community based organizations and a number of state public health departments began conducting and sponsoring OEND programs in 1996.¹¹ OEND programs typically make naloxone directly available to people who use opioids, outside of a medical setting, and include training on opioid overdose prevention, recognition, and response. The overdose response training includes seeking help from the emergency medical system, rescue breathing, administering naloxone, and staying with the victim until recovery or help arrives.

The articles representing program evaluations of OEND programs in Table 1 suggests that mortality from overdose can be prevented by providing overdose education and naloxone to a variety of participants, including people who used needle exchange programs and injected heroin,^{18, 23, 26–36} people using pharmaceutical opioids,^{37, 38} people who use opioids in treatment,^{24, 25} and the family and friends of people who use drugs.^{39, 40} These studies demonstrated that OEND trainings improved participants' knowledge of opioid overdoses and equipped them to administer naloxone safely and effectively when witnessing an overdose. One study suggested that participants reduced their frequency of injecting drugs and were more likely to enter treatment six months after naloxone training compared to baseline.³⁵ In Chicago, overdose deaths were reduced after the introduction of the OEND program.³³ An analysis that compared communities in Massachusetts with no OEND implementation to those with low implementation (1–100 people trained per 100,000 population) and high implementation (greater than 100 people trained per 100,000 population), demonstrated 27% and 46% reductions in opioid overdose mortality rates, respectively, after adjusting for community level demographic and substance use factors.⁴⁰

Effects of OEND Programs on Experiences and Attitudes of Participants

A number of articles support the feasibility of OEND programs. One concern that may inhibit naloxone prescribing is that potential bystanders or witnesses may not wish to

intervene in response to an overdose. Several studies confirm that witnesses are willing to take action to revive victims.^{19, 41–44} One study of people who use heroin showed that nearly every participant was willing to administer naloxone and perform rescue breathing if they had been trained.⁴⁵ The majority of participants from a needle exchange program who used heroin (92 percent) in an Australian study also reported a willingness to participate in an OEND program. Other studies assessed the willingness of participants to have naloxone used on them in an overdose event, with most participants responding that they would want naloxone to be administered to them in an overdose.⁴⁶

Because naloxone must be administered by a bystander, concerns that lay bystanders cannot accurately identify an opioid overdose and properly administer naloxone have been raised.⁴⁷ Several studies suggest that bystanders, including people who use opioids, are capable of recognizing an opioid overdose and administering naloxone.^{48, 49} In addition to targeting people who use opioids, some OEND programs focus on educating family members and/or bystanders who may witness an opioid overdose.⁵⁰ An evaluation of six OEND programs concluded that trained participants were more likely to recognize overdose scenarios and identify when naloxone administration was indicated compared to those who had not received training.⁴⁹ Trained respondents scored similarly to medical experts in accurately recognizing overdose scenarios and identifying instances when naloxone was indicated.⁴⁹ In a prospective study of overdose training and naloxone provision in 239 people who use opioids, participants had significant improvements in their knowledge of the risk factors for overdose, characteristics of an overdose, and the appropriate actions to reverse a potentially fatal overdose.²⁴ In Massachusetts, where a state sponsored OEND program has been in existence since 2007, methadone maintenance and medically supervised withdrawal (inpatient detoxification) patients have been successfully trained in overdose prevention, equipped with naloxone rescue kits, and rescued people in the community.³⁷ One study investigated the ability of participants to accurately share information about overdose prevention and naloxone administration with their peers and family, finding that they were able to successfully diffuse information from the program to others.⁵¹

Naloxone may be particularly beneficial in populations that may avoid or delay calling for emergency services (e.g. 911) when they witness an overdose due to fear of arrest for heroin or opioid analgesic possession, a pre-existing warrant, or because they are afraid of jeopardizing their housing.^{45, 52} While overdose education typically includes instruction on calling emergency services, trained bystanders may feel more capable to handle an overdose without help from paramedics or medical personnel. A survey of prospective OEND trainees in Baltimore reported that fewer subjects would call for help after naloxone training.⁵³ These concerns may be reduced through legislation and collaboration with law enforcement to shield bystanders from legal consequences when calling 911 or administering naloxone.³⁵

Medical Providers Willingness to Prescribe Naloxone

Prescribers in general medical practice have limited experience regarding naloxone for take-home use and potential misconceptions about naloxone. In one study of 571 physicians conducted from 2002 to 2003, 23% of those surveyed were aware of the option of prescribing take-home naloxone as an intervention to prevent the development of overdose

symptoms in people who use injection drugs.⁵⁴ Most physicians (54%) indicated that they would never consider prescribing naloxone to a patient who injected drugs, suggesting that providers may either be uncomfortable or lack knowledge about providing care for these patients.⁵⁴ This data was collected before pharmaceutical opioid overdose rates rapidly increased and community programs were well known, and did not assess physicians' willingness to prescribe naloxone to patients receiving prescription opioids. In another study conducted from 2001 to 2003, one-third of 363 nurse practitioners, physicians, and physician assistants surveyed said they would consider prescribing naloxone.⁵⁵ In a recent investigation of medical provider attitudes towards prescribing naloxone, providers expressed concerns that naloxone may condone riskier drug use.⁵⁶

Studies Comparing Routes of Naloxone Administration in Pre-Hospital Settings

The intranasal route of administration is not currently FDA approved, but its safety, convenience, and effectiveness (compared with IM naloxone) has been reported in controlled trials in pre-hospital settings.^{57–62} IN naloxone is available for off-label use and is the local standard of care in many emergency departments.⁶² In a study of people who used heroin, researchers reported a preference for IN naloxone administration over naloxone administered by needle injection due to its ease of use, reduced risk of blood-borne viruses, and less pain and risk from needle injection.⁴¹

In a study of adverse events after IM and IV naloxone treatment, by paramedics, the most common adverse events in 1,192 overdose episodes were withdrawal-related, including gastrointestinal discomfort, physical aggressiveness, tachycardia, shivering, sweating, tremors, confusion, and restlessness.⁶³ Overall, only 0.3% of patients were hospitalized for adverse events related to the administration of naloxone. Another study of 155 participants administered IM (n=71) or IN (n=84) naloxone involved no major adverse events.⁵⁹ Other studies have shown that while there is a longer mean response time and an additional dose of naloxone required when using IN naloxone, there were no additional adverse outcomes associated with its use.^{59, 64, 65}

Cost Effectiveness

Two studies, one in the US and one in Russia, estimated the cost-effectiveness of distributing naloxone to people who use heroin and concluded that naloxone distribution is cost-effective.^{66, 67}

DISCUSSION

Existing research suggests that training people who are at risk for overdose and their peers is a feasible and effective way to prevent mortality from overdose. The articles included in this review indicate that people are willing to be trained about the risk factors for an overdose and are capable of responding appropriately when witnessing an overdose. Both IM and IN naloxone have been shown to be effective at reversing an overdose in pre-hospital settings without considerable risks of adverse outcomes.

Some of the issues of implementing OEND programming into wider settings include medical providers' reluctance to prescribe naloxone. Medical providers may be concerned

about bystanders ability to accurately recognize an overdose and administer naloxone,⁴⁷ the cost of naloxone to patients,¹¹ and condoning riskier drug use.⁵⁶ Legal concerns may also be part of the reason for low engagement of prescribers in overdose education and naloxone prescription.⁶⁸ In a legal review of naloxone prescribing, Burris et al. concluded that if medical providers prescribe naloxone to people who use opioids they are doing so in a way that is consistent with state and federal laws regulating drug prescribing and the risks of malpractice are very low.⁶⁹

Between 2001 and 2013, 24 states and the District of Columbia (DC) enacted laws promoting the accessibility of naloxone in the community through limiting liability for prescribing, possessing, and/or administering naloxone.⁷⁰ Twenty-one of these states enacted laws promoting the prescription of naloxone to third parties, meaning those who are not themselves at risk for overdose, but may be in such a person's social network. In the absence of special legislation or standing orders permitting third party prescribing, providing naloxone to people who are not themselves at risk of overdose, but who may be friends or family of people who use opioids might be outside of the prescriber-patient relationship.⁶⁹

Concerns about police involvement may prevent individuals with criminal justice involvement or using non-prescription opioids from carrying prescribed naloxone with them and/or calling emergency services during an overdose.^{25, 31} Further regulatory or legislative action and community education/outreach to inform the public about their protections related to calling emergency services or administering naloxone may be necessary.⁷¹ States increasingly recognize the importance of bystanders' responding to overdose and are providing some immunity from arrest and/or prosecution for drug possession crimes and/or liability protection for administering naloxone.⁶⁹ Twenty-one states and the District of Columbia have enacted "Good Samaritan" provisions providing some protection from prosecution for people who provide help at the scene of an overdose.⁷⁰

The potential absence of medical personnel at naloxone reversals has led some to express concern that individuals who have been revived from overdose outside of a medical setting have less opportunity to enter substance use treatment.⁷² Advocates for naloxone distribution respond that it is an intervention that prevents death and allows for future possibility of recovery.⁷³ One study suggested education may promote treatment entry³⁵ Further work is needed about whether OEND or administration of naloxone increases treatment admissions for the individual trained or the person who overdosed.³⁵ Another common concern is that people may use larger doses of opioids, believing they can be rescued from an overdose but this is unlikely because of the unpleasant effects of naloxone on opioid dependent individuals, who rapidly experience symptoms of withdrawal with naloxone administration.⁷⁴

Implications for Medical Practice

In 2012, the American Medical Association and Massachusetts Medical Society issued endorsements of OEND programs.⁷⁵ Recently, OEND programs have expanded access to naloxone in many states, but a number of states with high drug overdose death rates remain without OEND programs.¹¹ Furthermore, OEND programs were originally established to address overdose people who inject heroin, but many others are at risk, including people

who take pharmaceutical opioids for pain. Additional risk groups have since been proposed as potential targets of overdose education and naloxone distribution (see Table 2).

While not addressed in the studies identified by this review, rising rates of pharmaceutical opioid use and overdose require novel prevention approaches to reduce risk. These approaches could include co-prescription of naloxone with opioids, insurance reimbursement for take-home naloxone, pharmacy dispensing of naloxone without a prescription, and over-the-counter naloxone distribution.¹³ More broadly, these interventions could be considered within the context of other opioid safety efforts, such as safe disposal of excess opioids,³⁸ prescription drug monitoring programs,⁷⁶ risk evaluation and mitigation strategies (REMS),⁷⁷ and abuse-deterrent medications.⁷⁸ New administration devices, such as Evzio, an auto-injector device, which was fast-tracked for approval by the FDA because of the severity of the opioid overdose epidemic, should be evaluated further for its effectiveness in pre-hospital settings and its limitations, such as cost and availability.⁷⁹

Opioid prescribers have a responsibility to assess the overdose risk in their patients and educate them about potential adverse events, including overdose.⁸⁰ Physicians have an opportunity to apply their clinical assessment skills to identify patients as candidates for overdose education and naloxone prescription based on known risk factors for overdose. A thorough clinical history would include asking patients about a history of prior overdose, chronic medical illness (pulmonary, renal or hepatic disease), drug use, incarceration history, and use of other sedating medications. Key elements of counseling patients may include not taking more milligrams or more frequently than prescribed, self-monitoring of functional status while on opioids, and letting others in one's family or social network know about the risks of overdose and what to do in the event of an overdose (e.g. calling 911). Prescribers should consider advising patients to secure opioids and other sedating medications, such as benzodiazepines, by keeping them locked up in the home to avoid diversion and to avoid sharing medications.⁸⁰

For patients with overdose risk, medical providers should prepare patients with instructions to follow in the event of an overdose. Prescribing take-home naloxone could be part of this preparation. The prescribing of naloxone should not be seen as a discrete event, but as part of an ongoing process that includes patient education, monitoring, and opioid dose adjustment.⁸¹ Because patients who have been prescribed naloxone are unable to use the drug on themselves, their peers and family members must be involved in overdose education and management training.⁷³

Barriers to prescribing naloxone may need to be overcome through efforts by physicians, pharmacists, policy-makers, patient advocates and health care systems. Pharmacies should consider stocking naloxone, intramuscular needles or nasal atomizers, and educational materials on administration. Patients may have to pay out-of-pocket for naloxone until insurance companies and public payers (e.g. Medicaid) cover naloxone, administration devices, and associated counseling/education costs. The Appendix includes several web resources produced by a variety of community-based OEND programs, government agencies, researchers, and activists which currently aim to educate medical providers about

their patients' risk of opioid overdose and provide information about prescribing naloxone. This list is not intended to be all inclusive or exhaustive, but provides a sample of resources available for medical providers interested in prescribing naloxone.

Gaps Identified and Further Research Needs

Based on current available evidence, prescribers should consider providing overdose education and naloxone in medical practice. Further study of barriers and facilitators to OEND in conventional clinical settings with more diverse populations of people at risk for overdose is needed. Future research should investigate how to select patients for naloxone prescription, how to engage patients and potential bystanders in overdose education and management training, the optimal breadth and depth of overdose education, the proper roles for different healthcare team members in disseminating OEND, the safety of take-home naloxone across a broad range of patient characteristics, and the reach and effectiveness of overdose education and naloxone prescription in traditional health care settings. These issues are particularly important since OEND programs may not meet the needs of all people who use pharmaceutical opioids due to the limited geographic availability of OEND programs, stigma against accessing community-based OEND programs, which have traditionally served people who use heroin and people who inject drugs, and costs of naloxone and related counseling or educational services. Access through traditional medical and pharmacy settings may offer some advantages including scale and insurance coverage. At the same time, clinical settings may not offer the degree of training or sensitivity to the needs of populations at risk demonstrated in dedicated community based programs. Additionally, more research should be conducted to understand what may be limiting medical providers' willingness to prescribe naloxone. Finally, more research using empirical data is needed to examine the cost-effectiveness of providing naloxone to patients treated with pharmaceutical opioids. While overdose education and naloxone distribution may be a key component of a public health effort to reduce opioid overdose deaths, our findings suggests further research is needed on the role of naloxone in conventional medical practice. Medical providers are in an ideal position to prescribe take-home naloxone to reduce mortality for opioid overdose amongst their patients.¹⁴ Data from observational, health services, and randomized controlled trials could further inform physician practice and establish a new standard of care, with regards to naloxone prescription to patients receiving opioids in medical practice settings.

Acknowledgments

We wish to acknowledge the Harm Reduction Action Center, Lisa Raville, Jane Kennedy, DO, Edward M. Gardner, MD, and Steve Koester, PhD for their assistance and thoughtful contributions.

FUNDING

Work on this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Numbers R34DA035952 and R21DA31041. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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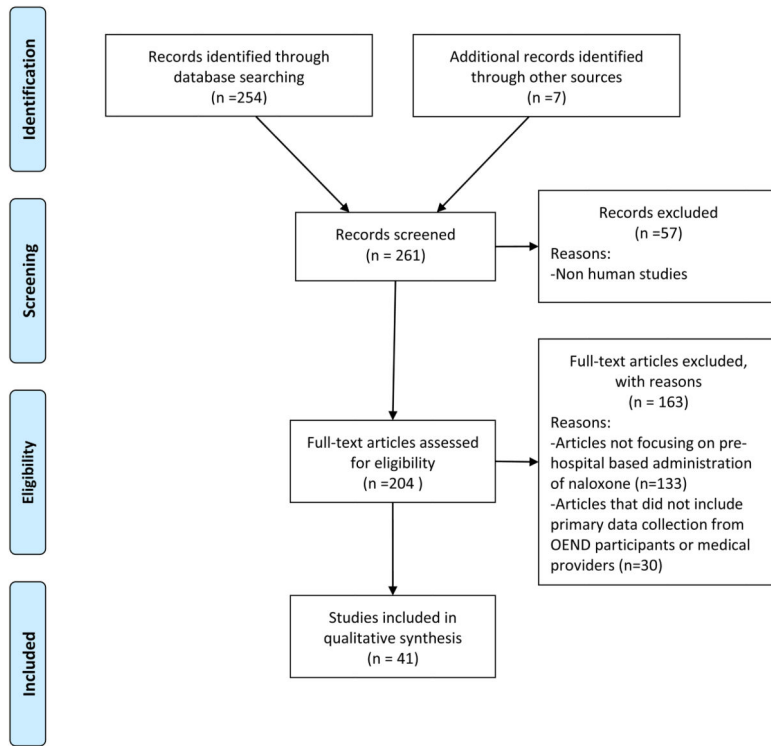


Figure 1.
PRISMA Flowchart of Included and Excluded Studies

Articles Included in Review

Table 1

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Evaluation of Overdose Education and Naloxone Distribution Programs						
Albert et al., 2011 ³⁸	North Carolina, USA	N/A	Overdose (OD) deaths in Wilkes County	Program description and evaluation	Determine if the OD death rate decreased over time after 5-strategy community-level overdose prevention program implementation	County OD death rate dropped from 46.6/100,000 to 29/100,000 with program implementation, but this occurred prior to the large rollout in the naloxone rescue kit portion of the intervention
Bennett et al., 2011 ²⁶	Pittsburgh, Pennsylvania, USA	426	Needle exchange program participants	Program description and evaluation	Describe the experiences of program participants	89 individuals reported administering naloxone in response to 249 OD episodes. In cases where naloxone was administered 96% of ODs were reversed.
Bennett et al., 2012 ²⁷	Wales, UK	525	521 opioid users, 4 non-opioid users	Repeated measure design	Determine the effectiveness of naloxone training on knowledge of opiate overdose and the willingness to use naloxone before and after training	Knowledge to recognize an OD, perceived confidence on treating an overdose, and willingness to carry out recommended procedures increased with training; Naloxone was used 28 different times (27 reversals and 1 fatality).
Doe-Simkins et al., 2009 ²⁸	Boston, Massachusetts, USA	385	Potential overdose bystanders	Program evaluation	Determine the feasibility of overdose prevention education and distribution intranasal naloxone as a public health intervention	After 15 months, follow up was made with 72% of program participants, with 50 reporting the use of naloxone to reverse an overdose; 74 opioid overdoses were successfully reversed.
Detmer et al., 2001 ¹⁸	Berlin, Germany and Jersey, Channel Islands	124	Opiate users attending a mobile health care project	Prospective cohort study	Determine the effectiveness of take-home naloxone in reversing opiate OD	22 out of 40 who reported back gave naloxone to 29 people, all of whom recovered (Berlin); it was appropriate in 90% of cases and caused abrupt opioid withdrawal in 34%; more risky consumption with availability of naloxone was not reported. In Jersey, 5 reported resuscitations with naloxone were reported, all recovered and no adverse consequences were reported.

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Eneen et al., 2010 ²⁹	San Francisco, California, USA	1942	People who inject drugs recruited from syringe exchange programs and other community sites	Program monitoring and evaluation	Determines outcomes of naloxone program	24% of naloxone recipients requested refills; of 399 ODs where naloxone was used, 89% were reversed; 83% attributed the reversal to the naloxone; 13% reported vomiting after administration, 9% reported anger or discomfort, 3 (<1%) reported seizures, and 4 did not survive.
Galea et al., 2006 ²³	New York City, NY, USA	25	People who inject drugs recruited from a syringe exchange program	Prospective cohort study (3 month follow-up)	Assess a pilot OEND program	11 of 22 participants who followed up at 3 months reported witnessing 26 ODs; naloxone was administered in 17 of these and all of these 17 live; at 7 witnessed ODs where naloxone was not given, 1 person died and one outcome was unknown, 15 of 20 participants felt comfortable using naloxone.
Strang et al., 2008 ²⁴	South East, South West, Midlands, and Northern Regions of England (UK)	239	Opiate users in treatment	Prospective cohort study (3 month follow-up)	Examine the impact of training in OD management and naloxone provision on participant knowledge and confidence and to assess subsequent management of OD	78% follow up with high retention of physical/behavioral characteristics of OD and actions to be taken at about 3 months; 17 OD occurred in 3 mo.; naloxone used 12 times with successful reversals; 4 of these were dissatisfied with being given naloxone (e.g. angry); When naloxone not used (n=6), 1 death occurred
Gaston et al., 2009 ²⁵	Birmingham and London, UK	70	Opioid dependent patients attending detoxification or drug treatment	Prospective cohort study (6 month follow-up)	Assess whether drug users are able to manage opiate overdose through peer interventions, including the administration of naloxone	Of 46 participants interviewed at baseline, 3 months and 6 months, 37 retained the naloxone that was prescribed them at 6 months, and knowledge of overdose recognition and intervention was strong. However, 30 participants did not consistently carry the naloxone with them and would not have it available in the event of an overdose.
Heller et al., 2007 ³⁰	New York City, New York, USA	1800	Syringe exchange program participants	Program evaluation	Describe the development of a naloxone distribution program	After 18 months, there were 162 OD reversals reported by 1800 program participants (9% reversal rate)
Lankenau et al., 2013 ³¹	Los Angeles, California, USA	30	OEND participants who use injection drugs	Program evaluation	Evaluate the effectiveness of two	30 ODs were witnessed after training, 29 victims recovered,

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Leece et al., 2013 ³²	Toronto, Canada	209	People who use opioids by any route	Program evaluation	OEND programs using closed and open ended interview questions OEND programs using closed and open ended interview questions OEND programs using closed and open ended interview questions Describe the first OEND program offered by a Canadian public health unit	After 8 months, 209 clients were trained and naloxone was administered in 17 ODs all of whom survived.
McAuley et al., 2010 ³⁹	Scotland	23	Drug users, friends and family of drug users	Program evaluation	Assess whether drug users and their friends and family could be trained to manage an OD and administer naloxone safely and effectively	3 ODs were witnessed, with 2 of the ODs reversed with naloxone. One OD led to death, as the participant did not have naloxone at the time. A majority of participants still had their naloxone after 6 months.
Maxwell et al., 2006 ⁵³	Chicago, Illinois, USA	319	Peer overdose reversals	Program evaluation	Describe and assess Chicago Recovery Alliance's OEND program	Out of >3500 multidosed vials of naloxone distributed, 319 reports of peer OD reversals obtained; 1 unsuccessful revival; 5 cases where the victim required 2 injections; 1 case of severe withdrawal symptoms, 1 case of seizures; 1/3rd of the ODs occurred in people who were reinstating heroin after a period of abstinence.
Piper et al., 2007 ⁵⁴	New York City, New York, USA	1004	Syringe exchange program participants and current or former drug users	Program description	Describe challenges to developing and running a naloxone distribution program and lessons learned	Challenges included political climate, prescription drug laws, recruitment into program, development of training methodologies, program evaluation, and evolution of program response to naloxone. Overcoming barriers to naloxone distribution programs include flexibility during program planning and implementation, developing feasible evaluation tools, and incorporating participant feedback.
Seal et al., 2005 ⁵⁵	San Francisco, California, USA	24 (in pairs)	People who injected heroin and had had prior heroin ODs	Prospective cohort study (6 month follow-up)	Determine the safety and feasibility of training people who inject heroin to perform CPR and administer naloxone in heroin ODs	20 OD events; naloxone was administered in 15; CPR and naloxone given in 6; CPR, 911 call and naloxone in 3 rescue breathing and naloxone in 3; naloxone in 3. The number of heroin ODs experienced by participants similar before and

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Lagu et al., 2006 ⁴³	Providence, Rhode Island, USA	329	Individuals who used heroin or cocaine by injection and non injection routes	Survey	administration method administration method	treatment by a peer, and 74% preferred intranasal naloxone 64% had witnessed an OD; 34.6% had overdosed; 88.5% willing to administer naloxone; 14% afraid to call for help
Piper et al., 2008 ⁴⁶	New York City, NY, USA	122	OEND program participants who requested a refill of naloxone	Survey	Describe the experience of people who used naloxone	Naloxone was administered 82 times; 83% lived; 82% were comfortable using naloxone; 86% would want naloxone administered on them if they were overdosing
Sherman et al., 2009 ⁵¹	Baltimore, Maryland, USA	25	Program participants who completed the training and had used naloxone to revive an OD victim	Qualitative interviews	Examine the diffusion of information and innovation among participants in the Staying Alive program.	Through peer diffusion of information, participants of the program were able to demonstrate correct responses to an OD and shared their knowledge with others who did not participate in the training.
Sherman et al., 2008 ⁵²	Chicago, Illinois, USA	31	Syringe exchange participants who had witnessed an OD in the past 6 months	Qualitative interviews	Determine what informed participants' choice in OD response.	Naloxone was administered in 58% of the last witnessed ODs. Participants' fear of legal consequences and a desire to save a life weighed into their decision on whether to administer naloxone and call emergency responders.
Tobin et al., 2009 ⁵³	Baltimore, Maryland, USA	85	Participants in the Staying Alive OEND program	Survey	Describe the results of pre- and post-test (6 month) evaluation surveys	51% witnessed an OD at baseline and follow-up. Pre training 911 call: 22 reversals with naloxone by 19 individuals. After training, inappropriate OD responses decreased and appropriate responses increased.
Wagner et al., 2010 ⁴⁸	Los Angeles, California, USA	69	Program participants who agreed to be enrolled in the study	Survey	Evaluate an OD prevention and response training program at 3 months	15% overdosed in past 3 mo; 49% witnessed OD in past 3 mo.; 22 participants responded to 35 ODs, 26 recovered, 4 died; response techniques included: staying w/victim (85%), naloxone (80%), rescue breathing (66%), and EMS call (60%)
Worthington et al., 2006 ⁸²	New York City, NY, USA	13	Opiate users and individuals who completed the Overdose Prevention and Reversal Program	Focus groups	Describe experiences with naloxone and the program	Participants were supportive of using naloxone to revive an overdosing friend or family

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Wright et al., 2006 ⁷⁴	United Kingdom	27	People with a past or current history of drug use, past or current history of homelessness, and experience with heroin OD	Qualitative interviews	To explore the acceptability and risk of peer naloxone use among homeless drug users	member. Barriers to take-home naloxone included difficulty. Barriers to take-home naloxone included difficulty. Barriers to take-home naloxone included difficulty. Barriers to take-home naloxone included difficulty. Participants preferred naloxone distribution in the context of training. Participants unlikely to use naloxone inappropriately or use more heroin as a result of naloxone for a range of reasons including cost considerations and desire to avoid withdrawal symptoms.
Willingness of Medical Providers to Prescribe Naloxone						
Beletsky et al., 2007 ⁵⁴	USA	588	Nationally representative sample of physicians in the American Medical Association master file	Survey	Physicians knowledge and willingness to prescribe naloxone to people who inject drugs	<1/4 had heard of naloxone prescription as an intervention; the majority of respondents reported they would not consider prescribing it; factors predicting a favorable attitude towards prescribing naloxone included fewer negative perceptions of people who inject drugs
Coffin et al., 2003 ⁵⁵	New York City, New York, USA	363	Random sample of prescription-authorized health care providers in New York City	Survey	Determine willingness to prescribe naloxone to patients at risk of an opioid OD	Willing to prescribe naloxone to patients at risk for OD=Total: 33% yes, 29% unsure; 37% no
Green et al., 2013 ⁵⁶	Connecticut and Rhode Island, USA	24	Emergency department, substance treatment, pain, and generalist providers	Qualitative interviews	Assess providers' support and concerns regarding take-home naloxone	Providers expressed concerns that naloxone may condone riskier drug use, may not be provided a proper education on how to use naloxone, and may be used as a medical providers' focal prevention effort
Tobin et al., 2005 ⁴⁷	Baltimore, Maryland, USA	176	Emergency Medical Services providers	Survey	Describe Emergency Medical Service providers attitudes towards take-home naloxone	56% responded that take-home naloxone training would not be effective in reducing deaths. Concerns included users' ability to administer naloxone appropriately, promotion of illicit drug use, and disposal of used needles.

Comparing Routes of Naloxone Administration in Pre-Hospital Settings

Article	Location	N	Population	Study Design	Question Addressed by Study	Summary of Key Findings
Barton et al., 2005 ⁶²	Denver, Colorado, USA	95	Adult patients in a prehospital setting with a suspected opiate OD, found down, or with and altered mental status who received intranasal (IN) naloxone	Prospective cohort study	Determine if intranasal naloxone is effective for suspected OD in prehospital settings	83% of patients who responded to naloxone (n=52) responded to IN and did not require intravenous naloxone
Buajordet et al., 2004 ⁶³	Oslo, Norway	1192	Patients who received naloxone by paramedics for heroin OD	Prospective observational study	Determine the frequencies and characteristics of adverse events related to out of hospital administration of naloxone by paramedics over a one year period	Adverse events of naloxone administration included 32% with confusion, 22% with headache, 9% with nausea/vomiting, 8% with aggressiveness and 6% with tachycardia. Serious adverse events from naloxone requiring hospitalization occurred in only three cases (0.3%).
Kelly et al., 2005 ⁵⁹	Victoria, Australia	155	Patients who received naloxone by paramedics	Prospective, randomized, unblinded trial of 2 mg intramuscular naloxone or 2 mg intranasal naloxone (in 5 mL)	Compare the effectiveness of intramuscular and intranasal naloxone	Response to intramuscular naloxone was more rapid than intranasal naloxone but required rescue naloxone was equivalent in both groups; For 74% of patients receiving intranasal naloxone, that intervention alone was sufficient to reverse OD
Kerr et al., 2009 ⁶⁴	Victoria, Australia	172	Patients requiring treatment for suspected opiate OD by ambulance services	Prospective, randomized, unblinded trial of 2 mg intramuscular naloxone or 2 mg intranasal naloxone (in 1 mL)	To assess whether IN naloxone is as effective as IM naloxone in treating suspected opiate ODs.	Mean response time, hospitalizations and minor adverse events were equivalent in patients administered IN or IM naloxone; More patients receiving IN naloxone required a rescue dose.
Merlin et al., 2010 ⁶⁵	Urban setting, USA	277	Patients who received naloxone by paramedics	Retrospective cohort study with chart review	Determine if intranasal naloxone is noninferior to intravenous naloxone	Intranasal naloxone was noninferior to intravenous naloxone at reversing the effects of opioid OD in terms of changes in Glasgow Coma Score and respiratory rate, but 42% of the intranasal naloxone recipients required redosing compared with 20% of the intravenous naloxone recipients.

Cost-effectiveness

Coffin et al., 2013 ⁶⁶	USA	N/A	Hypothetical 21 year old US heroin users	Cost effectiveness analysis	Estimate the cost effectiveness of distributing naloxone to comparing	In probabilistic analysis, 6% of OD deaths were prevented with naloxone distribution, equivalent to one death
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Table 2

Characteristics of Patients at Risk for Overdose

1	People who use multiple substances ⁸³⁻⁸⁶
2	Previous history of overdose ^{84, 85, 87, 88}
3	Recent release from a mandatory abstinence program or medical detoxification facility ⁸⁹
4	Recent release from a jail or prison ^{90, 91}
5	Higher-dose (>100 mg morphine equivalent/day) opioid prescription ^{92, 93}
6	Suspected or confirmed history of heroin or nonmedical use of opioids. ^{94, 95}
7	Methadone prescription ³⁷
8	Any opioid prescription to a patient with chronic pulmonary, renal or hepatic disease ^{92, 96, 97}
9	Have a mental health condition ^{98, 99}
10	Have ever been in drug treatment ¹⁰⁰
11	Unstably housed or homeless ²⁹
12	Concurrent use of opioids with alcohol, benzodiazepines, or antidepressants ^{84, 95, 101}

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