

Prescription Naloxone: A Novel Approach to Heroin Overdose Prevention

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The mortality and morbidity from heroin overdose have increased in the United States and internationally in the last decade. The lipid solubility allows the rapid deposition of heroin and its metabolites into the central nervous system and accounts for the "rush" experienced by users and for the toxicity. Risk factors for fatal and nonfatal heroin overdoses such as recent abstinence, decreased opiate tolerance, and polydrug use have been identified. Opiate substitution treatment such as methadone or buprenorphine is the only proven method of heroin overdose prevention. Death from a heroin overdose most commonly occurs 1 to 3 hours after injection at home in the company of other people. Numerous communities have taken advantage of this opportunity for treatment by implementing overdose prevention education to active heroin users, as well as prescribing naloxone for home use. Naloxone is a specific opiate antagonist without agonist properties or potential for abuse. It is inexpensive and nonscheduled and readily reverses the respiratory depression and sedation caused by heroin, as well as causing transient withdrawal symptoms. Program implementation considerations, legal ramifications, and research needs for prescription naloxone are discussed. [Ann Emerg Med. 2007; 49:172-177.]

0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2006.05.025

SCOPE OF THE HEROIN PROBLEM

The mortality and morbidity from heroin overdoses increased in the United States and internationally during the 1990s.¹⁻³ In Australia, the incidence of heroin overdose deaths increased from 1.3 per million in 1964 to 71.5 in 1997.^{4,5} Heroin-related deaths have been implicated in 9.4% of the total mortality in all persons aged 15 to 39 years in Australia. Heroin has become the leading cause of death among men aged 25 to 54 years in Oregon.^{1,6} In San Francisco, heroin overdose deaths represent the third leading cause of years of potential life lost.⁷ In 2002, the Drug Abuse Warning Network recorded 93,519 nonfatal heroin overdose-related emergency department (ED) visits in the United States, representing a 34% increase from 1995.⁸ The abuse of and overdose deaths related to prescription opioids have also increased, but there is little published research in this area.⁹

The morbidity of nonfatal heroin overdoses has only recently been described. In Australia, 33% of patients who had experienced a nonfatal heroin overdose were treated in an ED: 14% of these patients had sufficiently severe injuries, including trauma, burns, assault, pneumonia, or peripheral neuropathy, to require hospitalization.¹⁰ Other studies have demonstrated a significant decrease in cognitive function associated with nonfatal heroin overdoses.¹¹

The unique pharmacology of heroin makes it more likely than other opiates to cause a serious overdose. Heroin and other opiates produce their effects as agonists on the μ , κ , and Δ receptors in the central nervous system. μ_1 Receptors are responsible for most of the analgesic effects, and μ_2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, miosis, euphoria, and physical dependence.¹² Heroin is more lipid soluble than morphine and other opiates; it therefore crosses the blood-brain barrier within 15 to 20 seconds and achieves relatively high brain levels quickly.¹³ Sixty-eight percent of intravenous heroin is absorbed into the brain compared with less than 5% of intravenous morphine.¹⁴ This lipid solubility allows the rapid deposition of heroin and its metabolites in the central nervous system and accounts for the "rush" experienced by users and for the toxicity.

RISK FACTORS FOR HEROIN OVERDOSE

Long-term dependent intravenous heroin users who are not in substance abuse treatment are at the greatest risk of a heroin overdose.^{4,12} Heroin overdose victims are disproportionately male and commonly abuse benzodiazepines or alcohol.^{4,12,15} A recent period of abstinence, such as during incarceration or

substance abuse treatment, may lead to decreased tolerance and is a time of particular risk. Injection heroin users have 7 times the risk of death from an overdose during the first 2 weeks after their release from incarceration.^{12,16,17} Some authors have demonstrated a preponderance of older opiate users among fatal opiate overdoses, which may be explained by systemic disease processes or by a differing tolerance to the effects of respiratory depression and euphoria.⁵

Two recent intriguing studies of heroin overdose fatalities examined the morphine content of hair, which is a measure of the average use of heroin use over the last few weeks.^{18,19} Levels of morphine in the hair of fatal overdoses were much closer to those in a control group of abstinent former opiate users than to those of regular users, confirming that recent abstinence and low tolerance are related to death from heroin overdose.

More recent research has described other risk factors, such as an increased use of benzodiazepines or tricyclic antidepressants,²⁰⁻²² and issues with social marginalization such as polysubstance abuse, incarceration, or homelessness.²³⁻²⁸ It has also become clear that patients who have completed a course of naltrexone treatment or methadone detoxification programs are at particular risk.²⁹⁻³¹

OPPORTUNITY FOR INTERVENTION

Death from a heroin overdose most commonly occurs 1 to 3 hours after injection.³² Research has shown that most of these deaths occur in the company of other people and that medical help is not sought or is sought too late.^{7,33-35} The concern of police involvement has been a consistent barrier for the drug user to access the 911 system.^{23,36,37} In cases of nonfatal heroin overdoses, emergency medical services (EMS) are only contacted half of the time.^{7,34,36,38} The estimated mortality rate in heroin overdoses managed at home is 10%.¹²

PROVEN OVERDOSE PREVENTION

Novel approaches are needed to stem the epidemic of heroin overdose-related mortality and morbidity.^{4,32} Methadone maintenance decreases deaths from heroin overdose.^{23,39-45} In a meta-analysis, methadone maintenance reduced heroin users' risk of death by 75%, a reduction in mortality almost entirely caused by reductions in accidental overdose.⁴¹ French studies performed with buprenorphine maintenance have demonstrated similar benefits.⁴⁶⁻⁴⁸ A recent reduction in the heroin supply in Australia was associated with a reduction in fatal and nonfatal overdoses.^{49,50}

Clearly, increasing options for opiate substitution treatment with methadone and buprenorphine should be the cornerstone of any community's overdose prevention response. Unfortunately, there will likely always be some heroin users who are not ready for abstinence programs and will need other interventions.

Other strategies have emphasized reducing risk factors, improving the response of bystanders, medically supervising injecting rooms, and changing police policy concerning the arrest of overdose victims and witnesses.^{4,32,34,51-54} None of

these interventions have been methodically evaluated for their effectiveness in decreasing fatal and nonfatal heroin overdoses.

PRESCRIPTION NALOXONE

Starting in Europe and progressing to Australia and the United States, communities have begun to provide prescription naloxone for injection drug users.^{32,55-62} In 1995, naloxone was distributed to heroin users in Germany and England and is available over the counter in Turin, Italy.^{63,64} Surveys of heroin users demonstrate that most would favor the use of prescription naloxone.^{7,38,65} A third of health practitioners in one survey were interested in participating in a prescription naloxone program.⁶⁶

In the United States, naloxone was first distributed in 1999 through underground programs first in Chicago and then in San Francisco. There are an unknown number of underground programs, organized similarly to underground syringe exchange programs, in which activists and drug users operate informal networks to provide naloxone and education to heroin injectors. In March 2000, the California Medical Association and the San Francisco Department of Public Health recommended the use of prescription naloxone to injection drug users as part of a comprehensive overdose management program. In 2001, the San Francisco Department of Public Health sponsored a pilot research study that included opiate education and naloxone prescription.³⁷

In January 2001, New Mexico became the first state to encourage physicians to prescribe take-home naloxone to heroin-injecting patients. In addition, New Mexico's governor, Gary Johnson, led the implementation of legislation that releases individuals and medical professionals involved in administering and prescribing naloxone from medical liability. Connecticut and New York followed with laws that established standards for heroin overdose prevention programs and provided immunity from civil liability to nonhealth professionals by defining the use of naloxone as a first aid or emergency treatment.

There are now several prescription naloxone programs operating in the United States, including Chicago, San Francisco, northern New Mexico, Baltimore, New York, and Mendocino County, with thousands of injection drug users trained and prescribed naloxone during the last 7 years.⁶⁷⁻⁶⁹ As of February 2006, prescription naloxone programs have reported more than 900 episodes of peer reversal of a heroin overdose (Table).

LEGALITIES OF A NALOXONE PRESCRIPTION PROGRAM

Naloxone, a specific opiate antagonist available by prescription, is inexpensive and nonscheduled, has no abuse potential, and is effective at reversing the adverse effects of heroin.^{70,71} It is common practice for paramedics to use naloxone in most emergency medical systems. Prescription naloxone is considered an off-label use of the drug.⁶¹ There is

Table. Large and established naloxone prescription programs in the United States (February 2006).

City	Year of Establishment	Number of Trainings/Prescriptions	Number of Reported Overdose Reversals
Chicago	1999	4,600	416
New Mexico	2001	1,312	222
San Francisco	2003	650	141
Baltimore	2004	951	131
New York City	2005	938	73

Chicago: D. Bigg, written communication, March 2006; New Mexico: P. Fiuty, written communication, March 2006; San Francisco: E. Huriaux, written communication, March 2006; Baltimore: M. Rucker, written communication, March 2006; New York: S. Stancliff, written communication, March 2006.

considerable precedent for allowing physicians to provide patients or their families with other injectable preparations. Home prescriptions such as rectal valium and glucagon are dispensed with the expectation that a family member will administer the medication.

All prescriptions must be written by an appropriate health care physician, with a physician-patient relationship, appropriate recordkeeping, and proper labeling of the medication.⁶¹ All of the current naloxone programs that are sanctioned by their local department of public health in the United States (San Francisco, New Mexico, Baltimore, and New York) dispense naloxone in properly labeled kits contained in needle-proof hardened plastic containers or sunglasses cases.³⁷ Clear procedures for refilling the medication should be developed, and local pharmacies should be asked to stock naloxone and honor these prescriptions.

IMPLEMENTATION OF A NALOXONE PRESCRIPTION PROGRAM

Most naloxone prescription programs include an initial educational component. Several curriculums have been developed and are available online (<http://www.anypositivechange.org> and <http://www.harmreduction.org>). Our local experience in San Francisco indicates that shorter (15 to 20 minutes) sessions at syringe exchange program sites are superior to longer classroom venues. Important points for consideration in an educational component are included in the [Figure](#).

The intramuscular route of administration of naloxone is the most easily taught, and this route has been shown to be effective.^{72,73} The subcutaneous route is comparable to the intravenous route but poses some problems in education.⁷⁴ The intranasal route of administration was compared to the intramuscular route in one open-label out-of-hospital randomized trial. The intranasal group took slightly longer to achieve the end point of an adequate respiratory rate and had a higher need for rescue intramuscular naloxone, but the complication rate (agitation, vomiting, signs of withdrawal) was much lower in this group.⁷³ The intranasal route has drawbacks

1. Sites such as syringe exchange programs, drug treatment centers, and jails are logical institutions within which these programs can be placed.
2. Educational points for prescription naloxone education
 - A. The differentiation between the normal deep lethargy of opiate use (a deep nod) and an opiate overdose. The lack of a response to a sternal rub or other vigorous stimulation, blue lips, and absent breathing are all signs of a significant overdose requiring further treatment.
 - B. Rescue breathing should be taught and emphasized. The recovery position should be stressed if rescue breathing is not used. One study has demonstrated a modest decrease in hospitalization rates of nonfatal opiate overdose patients when bystander cardiopulmonary resuscitation was performed.⁸⁰
 - C. The use of other stimulation such as ice, milk, and amphetamines should be discouraged.
 - D. The importance of contacting EMS and the need for hospital evaluation after an overdose must be stressed because of the complications that can arise.
 - E. The short half-life of naloxone in comparison to heroin and other opiates should be highlighted. The importance of not using more heroin or other opiates within a few hours of revival should be stressed.
 - F. The proper dosing and administration of intramuscular naloxone should be taught.
3. The prescription should be provided by a licensed health care provider.
4. Medical records of the patient encounter and prescription need to be maintained.
5. Any prescribed medication must be properly labeled with the patient's name and instructions for use.
6. A system for medication refills should be established.
7. Primary care providers can be instructed in the use of prescription naloxone for patients who are still actively using heroin. Local pharmacies can be involved in honoring these prescriptions.

Figure. Implementation of a prescription naloxone program.

but could be a reasonable compromise in patients averse to using needles.

POTENTIAL ADVERSE OUTCOMES RELATED TO PRESCRIPTION NALOXONE

There are potential adverse outcomes related to prescription naloxone that must be evaluated. There has been concern that heroin users will increase their use because they have a

“parachute” in case of overdose.⁷⁵ The only published prospective evaluation of this concept demonstrated no increase in the frequency of reported heroin injections or rate of personal overdoses.³⁷ It could be argued that distributing naloxone may be construed as implicitly condoning the use of heroin and that the safety conferred by naloxone in the home may encourage people to start using heroin. However, there has been no documentation of this phenomenon.

There may be medical and legal implications of naloxone being used by people for whom it was not prescribed. In the Seal et al³⁷ study, only 15% of those treated were the patient for whom naloxone was prescribed. The half-life of naloxone is shorter than that of heroin; sedation and respiratory depression may recur in 15% of suspected heroin overdose patients treated with naloxone.⁷⁶ There may be reluctance on the part of active heroin users to administer naloxone to acquaintances because of the universally detested withdrawal reaction that accompanies its use. Naloxone treatment of opiate overdose is associated with common complications such as transient moderate to severe withdrawal (17% to 33%) and is associated with a small but consistent rate of complications such as seizures, pulmonary edema, and arrhythmias.^{72,76-78} Use of unsterile needles to administer naloxone may transmit HIV, hepatitis C, or other blood-borne infections.

Prescribing naloxone to a patient who has completed an abstinence program may send mixed signals, though it could be presented as a benevolent service to their peers. Finally, there are concerns that the 911 system will not be used after successful resuscitation, which is disconcerting because previous case series of nonfatal opiate overdoses have demonstrated a 5% to 12% prevalence of acute hospital admission.^{72,79} Two studies of prescription naloxone programs demonstrated that EMS was called in only 10% to 31% of cases in which an opiate overdose patient was successfully resuscitated.^{37,63} This incidence was lower than the 30% to 50% previously reported among witnesses of an opiate overdose that did not involve the use of prescription naloxone.

RESEARCH NEEDS

Current prescription naloxone programs have had little formal evaluation, and published reports are limited by small sample size, low response rates, significant selection bias, and no formal assessment of complications.⁷⁵ Structured, scientifically sound evaluations of prescription naloxone programs are needed as the number of programs grows. First, we need to evaluate whether these programs are achieving the intended goal of preventing heroin overdose fatalities. Such evaluation efforts need to include assessment of unintended negative consequences of the programs. If they are shown to be successful without undue negative consequences, we will need a second level of evaluation that involves assessing what are the best practices of such programs. These evaluations would provide important information to guide the implementation and design of existing and future prescription naloxone programs.

The international increase in heroin overdose has led public health authorities and investigators to seek innovative methods of decreasing its morbidity and mortality. Communities should implement proven heroin overdose tactics such as increasing treatment options for methadone or buprenorphine maintenance as their cornerstone strategy. When properly implemented, prescription naloxone can be a legal and safe program. As a complement to opiate substitution treatment, prescription naloxone programs should be considered a standard part of care and should be implemented in vulnerable populations. Their effects on mortality, on complication rates, and on patterns of consumption of opiates should be carefully studied.

Supervising editor: Richard D. Dart, MD, PhD

Funding and support: The authors report this study did not receive any outside funding or support but discloses that KAS receives compensation for AED medical direction from American Health and Safety Training, Inc.

Publication dates: Received for publication February 7, 2006. Revisions received March 30, 2006, and April 25, 2006. Accepted for publication May 23, 2006. Available online July 12, 2006.

Reprints not available from the authors.

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