Abstract:
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.

Prescription Naloxone:
A Novel Approach to Heroin Overdose Prevention

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Abstract
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A Novel Approach to Opiate Overdose Prevention

The mortality and morbidity from heroin overdoses have increased both 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 both the "rush" experienced by users and the toxicity. Risk factors for fatal and non-fatal heroin overdoses such as recent abstinence, decreased opiate tolerance, and poly-drug 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 at home in the company of other people and most commonly occurs one to three hours after injection. 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 with no agonist properties and no potential for abuse. It is inexpensive, non-scheduled 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.

Prescription Naloxone
A Novel Approach to Heroin Prevention

Scope of the Heroin Problem

The mortality and morbidity from heroin overdoses increased both in the United States and internationally during the 1990's.[1-3] In Australia, the incidence of heroin overdose deaths has 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 15-39 years of age in that country and is the leading cause of death among men aged 25-54 years in Oregon.[1, 6] In San Francisco, heroin overdose deaths have represented the third leading cause of years of potential life lost.[7] In 2002, the Drug Abuse Warning Network recorded 93,519 non-fatal heroin overdose related emergency departments visits in the United States representing a 34% increase from 1995.[8] There has been a recent increase in the abuse of and overdose deaths related to prescription opioids but there have been little research in this area.[9]

The morbidity of non-fatal heroin overdoses has only recently been described. In one study in Australia, 33 percent of patients who had experienced a non-fatal heroin overdose ended up needing treatment in an emergency department. Fourteen percent of these non-fatal heroin overdoses 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 non-fatal 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 mu, kappa, and delta receptors in the central nervous system. Mu_1 receptors are responsible for most of the analgesic effects, and Mu_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 both the "rush" experienced by users and 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. Heroin overdose victims are disproportionately male, are commonly also abusing 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 has been shown to be a time of particular risk. Injection heroin users have seven times the risk of death from an overdose during the first two weeks after their release from incarceration.[12, 16 17] Some authors have demonstrated a preponderance of older opiate users among fatal opiate overdoses in there studies and this 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 people who had died from an overdose, examined the morphine content of the 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 are at particular risk as well as methadone detoxification programs.[29-31] Some authors have suggested that the preponderance of older opiate users among fatal opiate overdoses may be explained by systemic disease processes or by a differing tolerance to the effects of respiratory depression and euphoria.[5]

Opportunity for Intervention

Death from a heroin overdose most commonly occurs one to three 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 non fatal heroin

overdoses, emergency medical services 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 to heroin overdose prevention are needed to stem the epidemic of heroin overdose-related mortality and morbidity.[4, 32] Methadone maintenance has clearly been shown to decrease deaths from heroin overdoses[23, 39-45] In a meta-analysis, methadone maintenance reduced heroin users risk of death by 75%, a reduction in mortality almost entirely due to 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 has been demonstrated to reduce 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 not ready for abstinence programs that will need other interventions.

Other strategies have emphasized the reduction of risk factors, improving the response of bystanders, medically supervised 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 non-fatal heroin overdoses.

Prescription Naloxone

Starting in Europe and progressing to Australia and the United States, communites have begun to provide prescription naloxone for injection drug users (IDU's).[32, 55-62] In 1995, naloxone was being distributed to heroin users in Germany and England and available over the counter in Turin, Italy.[63, 64] Surveys of heroin users have demonstrated that most would favor the use of prescription naloxone.[7, 38, 65] A third of health practitioners in one survey reported being 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 IDU's 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 US 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 provided immunity from civil liability for licensed

health care practitioners to prescribe, dispense, distribute, and administer opioid antagonists to drug users to prevent overdose deaths.

There are now several prescription naloxone programs operating in US localities, including Chicago, San Francisco, northern New Mexico, Baltimore, New York, and Mendocino County with thousands of injection drug users trained and prescribed naloxone over the last 7 years.[67-69] As of February 2006, prescription naloxone programs have reported over nine hundred episodes of peer reversal of a heroin overdose. (See Table 1)

Legalities of a Naloxone Prescription Program

Naloxone, a specific opiate antagonist available by prescription, is inexpensive, non-scheduled, has no abuse potential and is effective at reversing the adverse effects of heroin. [70, 71] Currently, it is common practice for paramedics to use naloxone in most EMS systems. Prescription naloxone is considered an off label use of the drug.[61] There is considerable precedent for allowing doctors to provide patients or their families with other injectable preparations. Home prescriptions such as rectal valium (diastat) 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 provider with a provider client relationship, appropriate record keeping, as well as proper labeling of the medication.[61] All of the current naloxone programs that are sanctioned by their local department of public health in the US (San Francisco, New Mexico, Baltimore, and New York) are dispensing properly labeled kits made out of

needle proof hardened plastic containers or sunglass cases with the naloxone and syringes.[37] Clear procedures for refilling the medication should be developed and local pharmacies should be asked to stock naloxone to 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. (www.anypositivechange.org and www.harmreduction.org) Our local experience in San Francisco has led us to believe that shorter (15-20 minute) sessions at syringe exchange program sites are superior vehicles for education than longer classroom venues. Important points for consideration in an educational component are included in Table 2.

The intramuscular route of administration of naloxone is the most easily taught and this route has previously been shown to be effective.[72, 73] The subcutaneous route has been demonstrated to be comparable to the intravenous route but poses some problems in education.[74] The intranasal route of naloxone administration was compared to the intramuscular route in one open-label prehospital 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 thus has drawbacks but could be a reasonable compromise in those who may be averse to using needles.

Potential Adverse Outcomes Related to Prescription Naloxone

There are potential adverse outcomes related to prescription naloxone that must be evaluated in any program. There has been concern that heroin users will increase their use because they feel like they have a "parachute" in case they 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 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 Seal's study, only 15% of those treated were the prescribing patients.[37] The half life of naloxone is shorter than that of heroin and there is a concern that sedation and respiratory depression has been shown to recur in 15% of suspected heroin overdose patients treated with naloxone.[76] There may be some 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 utilized in the setting of a successful resuscitation. This is disconcerting because prior case series of non-fatal opiate overdoses have demonstrated a 5-12% prevalence of acute hospital admission.[72, 79] Two studies of prescription naloxone programs have demonstrated that EMS was called in only 10-31% of cases of opiate overdose patient that were successfully resuscitated.[37, 63] This was lower than the 30-50% previously reported among witnesses of an opiate overdose that did not involve the use of prescription naloxone.

Research Needs

It has been pointed out that current prescription naloxone programs have had little formal evaluation and that published reports have had 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 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 could provide important information to guide the

implementation and design of existing and future prescription naloxone programs.

Conclusion

The international increase in heroin overdoses 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 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.

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Table 1: 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

Personal Communication: Dan Bigg, Chicago; Phillip Fiuty, New Mexico; Emalie Hurieux, San Francisco; Monique Rucker, Baltimore; Sharon Stancliff, New York.

Table 2
Implementation of a Prescription Naloxone Program

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, 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 non fatal opiate overdose patients when bystander CPR was performed.[80]

   C. The use of other stimulation such as ice, milk, and amphetamines should be discouraged.

   D. The importance of contacting emergency medical services 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.

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 patients 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.