

PROJECT LAZARUS

Wilkes County, North Carolina

Policy Briefing Document

*Prepared for:
North Carolina Medical Board*

*In advance of:
Public Hearing Regarding Prescription Naloxone*

Wednesday, November 14, 2007

Raleigh

If you ever get in a meeting with some professional-type people, tell 'em that, you know, people like us—no, we're not professionals, but if we have it at hand we can save somebody's life with this stuff [naloxone] . . . it's a lifesaver, there's no question.

From a program participant in Chicago
Maxwell S, et al. J Addict Dis. 2006;25(3):89-96.

EXECUTIVE SUMMARY

- **What is the target population for Project Lazarus? What will the NC program look like?** [Page 3]
In Wilkes County, 25 or more residents have died annually in the past several years from unintentional drug overdoses. The majority of deaths were due to respiratory depression from unintentional opioid overdoses (technically called *unintentional poisoning*). **Project Lazarus** is a pilot program in Wilkes County, NC for the prescription and distribution of intranasal naloxone (a drug that reverses respiratory depression that occurs from opioid overdoses) for the purpose of preventing death. While parallel measures are being undertaken to improve the prescription of opioids for pain management and to reduce the illicit abuse of these essential medications, Project Lazarus is aimed at reducing fatalities among 13 subpopulations that are at increased risk of abusing or misusing narcotics and dying from a fatal drug overdose. Project Lazarus includes a 20 minute structured educational intervention that teaches how to : 1) recognize the signs of an opioid overdose, 2) understand the importance of calling 911, 3) perform rescue breathing, 4) administer intranasal naloxone, and 5) obtain treatment of substance abuse and misuse. The Project also includes a protocol for documenting the medical encounter (following the paradigm for influenza vaccination) and provides a kit containing pre-filled syringes of naloxone with adapters for nasal administration.
- **Are there groups who are opposed to the program and why?** [Page 10]
No organized groups have voiced opposition to prescription naloxone in North Carolina. Despite initial concerns in other cities and countries that the distribution of medications to reverse respiratory depression after an unintentional drug overdose, no evidence of increased abuse of street drugs has been documented where these programs are in place.
- **By our approval/allowing this program to go forward are we abetting illicit drug use?** [Page 10]
Project Lazarus is not abetting illicit drug use. Experiencing an overdose is a traumatic event that elicits complex emotional reactions. There is evidence to suggest that overdose survivors are receptive to behavior change and that surviving an overdose may serve as an opportunity to discuss drug treatment options with the victim, family and peers. Other prescription naloxone programs in the US have observed decreases in injection drug use and increased entry into substance use treatment in the month following naloxone administration.
- **Are there unintended deleterious effects of “approval?”** [Page 11]
There are relatively few deleterious effects from the administration of naloxone after a drug overdose. Adverse events associated with naloxone administration are consistent with acute opioid withdrawal, which, albeit unpleasant, are better than death. Return of respiratory depression may occur with long-acting opioid and controlled-release formulations. Education and supplemental naloxone vials are provided to mitigate this risk.

- **What is the narcotic overdose rate for NC and/or the proposed service area? How many lives/hospitalizations would be saved by this program?** [Page 13]

Wilkes County has a rate of accidental opioid poisoning deaths nearly *five* times greater than the national average, and *three* times higher than the state average. In 2005, 18 deaths resulted in a rate of 27.4 per 100,000 per year; 20 deaths reported in 2006 gave a rate of 30.5 per 100,000 per year, predominately due to methadone. In 2007, the mortality rates have been similar, with 13 accidental opioid poisoning deaths in Wilkes County, with 2 pending investigations. The cost of inpatient hospitalizations alone for opioid poisoning in North Carolina is more than \$20 million per year, half from uninsured and Medicaid patients. For *each* overdose prevented through Project Lazarus, there will be a \$20,000 to \$30,000 savings in medical expenses and lost productivity, suggesting high potential for a favorable cost-effectiveness benefit.

- **What is the legal status of prescription naloxone programs in North Carolina?** [Page 15]

Prescribing naloxone to opioid drug users in North Carolina is fully consistent with state and federal laws regulating drug prescribing. Any legal risks in distributing naloxone in this state are not substantial and can be mitigated by informed program design; the risks of malpractice liability are consistent with those generally associated with providing healthcare.

What is the target population for Project Lazarus? What will the NC program look like?

Project Lazarus, Wilkes County, North Carolina

- Context
 - Increasing number of deaths from unintentional overdoses of prescription opioids in Wilkes County.
 - Chronic Pain Initiative balances adequate pain management with prevention of harm from prescription opioid use.
- Educational intervention

20 minute educational training that includes:

 - 1) recognizing signs and symptoms of opioid overdose
 - 2) understanding the importance of calling 911
 - 3) learning rescue breathing
 - 4) the appropriate use of naloxone
 - 5) options for substance use treatment
- Kit with 2 doses of 1 mg/mL naloxone hydrochloride in pre-filled needleless syringes, nasal adaptors, instructions, referrals to local substance abuse/dependence treatment
- Following influenza vaccine paradigm, record keeping for medical encounter
- Target populations: medical and nonmedical users of prescription opioids, with known risk factors for opioid poisoning.
- Evaluation of pilot program

Context

In Wilkes County, the prescription naloxone program, **Project Lazarus**, is one component of a multifaceted response (the Chronic Pain Initiative, see below) to an epidemic of the misuse and abuse of prescription opioids that has resulted in an unprecedented increase in fatal unintentional poisonings. Fatal drug overdoses occur from legally prescribed narcotics, such as fentanyl, hydrocodone, methadone and oxycodone, as well as from street drugs such as cocaine and heroin. In this document, the *misuse* of a narcotic refers the inappropriate medical use of a prescribed narcotic by a patient (such as non-adherence when a patient does not follow a prescriber's recommended usage/dosage). *Abuse* always refers to the nonmedical (i.e., recreational) use of a narcotic. Both legal prescription and illegal "street" drugs can be abused.

The **Chronic Pain Initiative** is sponsored by the Northwest Community Care Network. The other components of the response include: case management of and data collection on patients initiating opioid therapy, establishment of a pharmacy home system, collaboration with mental health planning, better management of patients in the emergency department, utilization of the controlled substances reporting system, and physician education, including development and dissemination of a toolkit on opioid prescribing and pain management for prescribers.

The goals of the Chronic Pain Initiative are to: decrease ED (emergency department) utilization by drug seekers, decrease use of multiple prescribers and multiple pharmacies, improve HCP (healthcare provider) efficacy in chronic pain management, encourage appropriate pain clinic referrals, encourage co-management model for partnership with pain clinic, reduce number of unintentional poisonings from drug overdoses, and decrease costs associated with improper use of prescription opioids. It is our intention to develop a reproducible, comprehensive approach to chronic pain management that may be duplicated by others in North Carolina.

Target Populations

Just as the physiological and anatomical bases for pain and addiction share common pathways in the central nervous system, the community-level response to prescription opioid use problems must address pain and abuse/addiction simultaneously. The distinction between medical and nonmedical use of prescription opioids can change overtime for a given individual. A patient with a legitimate acute pain condition could keep leftover opioid medication for at a later painful condition; at that point a legitimate pain patient is considered to be abusing the medication. Patients with history of alcohol use disorder may respond well to opioid therapy and complete medication use without untoward incident. While illicit drugs (heroin, cocaine, methamphetamine) may be involved in a poisoning event, it is just as likely that legal prescription medications (benzodiazepines, TCA and SSRI anti-depressants) will also be implicated.

The treatment of severe chronic pain is now clearly recognized by the medical community as a compelling need in the practice of medicine. The patient population is broad, as the recipients of pain management should not be restricted to those with terminal cancer or who are under the care of a hospice program. Opioids are the mainstay of pharmacologic management of moderate to severe chronic pain in the United States. In recognition of their vitally important place in medical practice, opioids for use in pain management and the pharmacotherapy of opioid dependence have been placed on the World Health Organization's List of Essential Medicines (Herget 2005). Nevertheless, it is also recognized that chronic pain is often difficult to treat in the outpatient setting. Although prescribers should follow the pain management recommendations posted by the NC Medical Board on their website (also, Trado 2004), it does not guarantee that their patients will follow instructions or that their patients do not also have a comorbid dependence disorder that greatly enhances the complexities encountered by the medical community. These two very different issues can lead to both misuse and abuse of the prescribed drug, sometimes at the same time or at different times. Examples of misuse and abuse are when a patient experiences inadequate pain control and takes more tablets than prescribed (misuse) or takes part of the prescription as prescribed and then uses the remaining pills for nonmedical reasons (abuse). To complicate the situation further, people with abuse/dependence disorders frequently suffer from severe chronic pain thus complicating the strategies for treating both conditions. Effective strategies for opioid

therapy in patients with a history of substance use have been elaborated (Schnoll and Weaver 2003), and healthcare providers have a duty to reduce painful conditions in such patients.

In addition to differences in patient characteristics that complicate pain management in the outpatient setting, there are pharmacological differences in the pain medications that can affect the central nervous system. Prescribed opioids that control pain are formulated to be short acting/immediate release (e.g., codeine, Vicodin®, Dilaudid®, and Percocet®) and long acting/controlled-release analgesics (e.g., OxyContin®, Kadian®); some have short half lives while others can remain functioning in the body as a potential contributor to respiratory depression for days after the dose is taken and the analgesic effect has worn off (e.g., methadone). In short, strategies to reduce the potential for fatal drug overdoses much take into account differences in both patients and narcotics.

A summary of the target population is provided in Table 2, page 8.

An investigation into the source of medications implicated in prescription opioid poisonings was conducted by the Injury & Violence Prevention Branch of the NC Division of Public Health, for 244 deaths that occurred between 1997-2001. While the source of prescription drugs was unknown for 56% of decedents, the medication was prescribed for the victim in at least 38% of cases. A chart review of fatal methadone poisonings by the state health department in 2001 revealed that both prescribed and illicitly obtained were implicated as the source of the lethal dose (Sanford 2004), see Table 1. The analysis also showed that the source of the methadone implicated in fatal poisonings was rarely from methadone maintenance treatment programs.

Table 1. Sources of Methadone Implicated in Poisoning Deaths, North Carolina, 1997-2001 (n=92)

Prescribed to decedent	79%
Prescription written for someone other than decedent	12%
Obtained on the street	3%
Combined prescription and street methadone	5%

Source: Sanford 2004

While some decedents may have deceived healthcare personnel to obtain a prescription, it is likely that many, if not most, of these deaths were among patients with legitimate pain concerns, and their deaths were due to idiosyncratic reactions, comorbid conditions, medication handling errors, or incorrect administration. Further, anecdotal information from Wilkes County supports this hypothesis. For example, the wife of one decedent who died from a methadone overdose reported that her husband was a patient under the care of a physician who had prescribed methadone and had no history of substance abuse. He took extra doses of medication prior to his death to compensate for inadequate pain control.

For these reasons, we have decided to target prescription naloxone to particular populations of medical and nonmedical users of prescription opioids. Table 2 lists 13 potential indications for receiving naloxone prescription to prevent poisoning mortality. Each indication can be interpreted as a different subpopulation, defined by known risk factors, who have an elevated chance for opioid poisoning.

About Naloxone

Naloxone is a mu-opioid receptor antagonist. It competitively displaces opioid agonists, thereby restoring respiration rates to pre-exposure levels. Naloxone hydrochloride is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic opioids, and certain partial opioid antagonist analgesics. Naloxone is used routinely in medical care: 1) by emergency medical staff, including by EMS and in emergency departments; 2) for reversing the effects of anesthesia; 3) in mixed entity abuse-resistant formulations with opioid agonists for pain and addiction management. Naloxone has no psychoactive properties and is not a controlled substance. Acute administration does not appear to cause long-term changes in endogenous opioid signaling. Naloxone hydrochloride is available as a clear liquid suspension and can be injected or administered nasally. Project Lazarus has chosen to provide naloxone with nasal adaptors because many decedents are not suspected to have a history of injection drug use. The only contraindication for naloxone is in patients who are known to be hypersensitive to it. Naloxone is not effective against non-opioid drugs.

Structure of Prescription Naloxone Program

At the current time, a documented medical encounter is needed to prescribe and dispense naloxone in North Carolina, the same as it is for any other prescription medication. Table 2 describes settings for the medical encounter. Following the paradigm for influenza vaccination, a one page intake form will be used to collect background information on the patient, modeled on patient history forms approved for use in other states: basic identifying and demographic information, risk factors for overdose, medication allergies, and any other information deemed relevant, will be documented. The educational component of the medical encounter consists of five learning objectives, presented on page six. Prescribers and trainers will be instructed on the appropriate use of naloxone, indications, and required record keeping. Following models used in other states, the educational messaging can be completed by staff other than the prescriber or by the licensed health care provider directly. This education takes approximately 20 minutes. The education consists of: 1) recognizing the signs of an opioid overdose, 2) understanding the importance of calling 911, 3) learning rescue breathing, 4) the appropriate use of naloxone, and 5) options for substance use treatment. Upon completion, the patient will receive the naloxone kit (in accordance with North Carolina dispensing laws), instructions on the use of naloxone and referrals to local substance abuse/dependence treatment services. This educational intervention has been designed in accordance with a review of applicable North Carolina statutes and case law regarding medical practice and dispensing of prescription medications (Burriss 2007).

An evaluation of existing programs in the United States revealed that those who had been trained via a prescription naloxone program had greater knowledge of the dangers of opioid use: 85.2% correct responses for overdose knowledge (versus 68.3% for untrained) and 84.6% correct responses for naloxone administration knowledge (versus 69.3% for untrained) after the 20 minute educational intervention (Green, Heimer et al. 2007). These data show that prescription naloxone programs can improve knowledge of opioid poisonings, as well as provide participants with tools to reduce harm associated with the use of these medications.

The patient will not be able to administer naloxone to him/herself. Following the model for insulin injection in diabetic patients, education of peers and family members is of critical importance. Broad

community-based education campaigns are also being considered to deliver the key points from the five-part educational message described above. This can include use of public service announcements, media campaigns, and other tools. Written and illustrated instructions will also be included with the naloxone kit.

Most other prescription naloxone programs distribute vials of naloxone hydrochloride suspension with intramuscular safety syringes. Since the target population in Wilkes County is believed to include many non-injection drug users, we have opted for an intranasal delivery system. The naloxone will come in a single dose pre-filled syringe with 1 mL of a 1 mg/mL solution. The recommended dose will be 0.5 mL of in each nostril, for a total of 1 mg of naloxone administered. Intranasal delivery systems are currently being used by prescription naloxone programs in New Mexico (Lieving 2007). Participants will be emphasized to report any reversal; when a participant returns for a refill (up to three), the encounter and use will be documented.

Previous Experience

Prescription naloxone programs have been implemented in European countries since 1995 (Dettmer, Saunders et al. 2001); based on the positive results of these initial sites, naloxone became available over the counter in parts of Italy for preventing fatal opioid poisonings. Since then, prescription naloxone programs have started in Australia (Lenton and Hargreaves 2000) and the North America. In the United States, programs currently exist in at least nine states, several of which have been evaluated in the peer-reviewed literature, and most receive funding and support from state health departments: California (Davidson, McLean et al. 2003; Seal, Thawley et al. 2005), Connecticut, Illinois (Maxwell, Bigg et al. 2006), Maryland (Sporer and Kral 2007), Massachusetts, New Mexico (Sporer and Kral 2007), New York (Galea, Nandi et al. 2006; Piper, Rudenstine et al. 2007), Pennsylvania and Wisconsin.

Evaluation

Project Lazarus will be evaluated in the context of the Chronic Pain Initiative. Gross changes in opioid poisoning mortality should not be judged to be due to Project Lazarus alone. Evaluation measures for different components of prescription naloxone programs have been used in scientific studies, including: review of medical examiner data, interviews with program participants, tests of knowledge retention, health service (EMS/ED) utilization, attitudes of service providers, number of doses handed out, number of documented reversals, changes in drug use, and entry into treatment. Which of these measures will be of most use will be dictated by the final structure of Project Lazarus. Evaluation will be conducted in conjunction with researchers in the Department of Epidemiology at the UNC School of Public Health, and with the assistance of existing programs around the United States and the Harm Reduction Coalition.

For a concise overview of the implementation of prescription naloxone programs, please see:

Sporer, K. A. and A. H. Kral (2007). "Prescription naloxone: a novel approach to heroin overdose prevention." *Ann Emerg Med* **49**(2): 172-7.

For details on the workings of a pilot program, please see:

Seal, K. H., R. Thawley, et al. (2005). "Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study." *J Urban Health* **82**(2): 303-11.

Table 2. Potential indications for prescription naloxone, opioid poisoning risk factors, and setting for medical encounter.

	Potential Indication/Patient population	Documentable Risk Factor for Poisoning	Setting for Medical Encounter
1	Emergency medical care for opioid poisoning	Increased risk for subsequent accidental poisoning and self-harm	Hospital emergency department or emergency medical services
2	Suspected illicit or nonmedical opioid user	Risk for multiple drug use; continued (multiple) drug use; reduced opioid tolerance among inpatients	Primary care provider, hospital HCP, county health department
3	High-dose opioid prescription (> 100 mg of morphine equivalence/day)	Patient incorrectly administers opioid resulting in higher risk of toxic levels (e.g., <i>prn</i> use of long-acting opioid)	Primary care provider, pain management clinic, hospice
4	Any methadone prescription to opioid naïve patient	Low threshold for overdose; inexperience with long-acting opioids	Primary care provider, pain management clinic, hospice
5	Any opioid prescription and smoking/COPD/emphysema or other respiratory illness or obstruction	Increased risk of respiratory depression due to comorbidities	Primary care provider, pain management clinic, hospice
6	Any opioid prescription for patients with renal dysfunction, hepatic disease	Prolonged and/or increased serum concentrations of opioid due to decreased metabolism and/or excretion	Primary care provider, pain management clinic, hospice
7	Any opioid prescription and known or suspected concurrent alcohol use	Additive effect of multiple CNS depressants	Primary care provider, pain management clinic, hospice
8	Any opioid prescription and concurrent benzodiazepine prescription	Additive effect of multiple CNS depressants	Primary care provider, pain management clinic, hospice
9	Any opioid prescription and concurrent SSRI or TCA anti-depressant prescription	Increased toxicological risk for opioid poisoning; higher risk for substance use and self-harm	Primary care provider, pain management clinic, hospice
10	Released prisoners	Relapse to/initiation of nonmedical opioid use; reduced opioid tolerance; risk for multiple substance use	Prison medical system
11	Release from opioid detoxification or mandatory abstinence program	Relapse to nonmedical opioid use; reduced opioid tolerance; risk for multiple substance use	Detoxification clinic, referral to HCP
12	Voluntary request	Perceived risk for opioid exposure	County health department, primary care provider, street outreach
13	Patients entering methadone maintenance treatment programs (for addiction or pain)	Increased risk for poisoning in first month; risk for multiple substance use	Licensed methadone maintenance treatment programs

Learning Objectives and Educational Message Components

Approximately 20 minutes

Objective 1: Learn how to recognize an opioid overdose

- Signs and symptoms of an opioid overdose (poisoning)
- Differentiating between opioid and non-opioid poisonings
- Risk factors for opioid poisoning
- Dispel street myths for dealing with an overdose

Objective 2: Recognize the importance of calling 911

- Why it is important to call 911
- Reinforce why to stay with patient
- Learn what information to give to EMS

Objective 3: Learn rescue breathing

- Rescue position
- How to clear an obstructed airway
- Technique for rescue breathing
- How many breaths to give
- Evaluation of breathing

Objective 4: Learn how to administer naloxone

- Kit contents
- Preparing the syringe and nasal adaptor
- How to administer
- Reinforce importance of staying with victim
- When to administer a second dose
- Possible adverse events of naloxone administration to opioid dependent individuals
- Obtain prescription and dispense naloxone
- Making an overdose response plan
- Reporting an opioid reversal
- Getting a refill

Objective 5: Learn options for drug treatment

- Know how to identify when opioid use becomes problematic
- Understand treatment options for drug abuse/dependence
- Identify local entities that provide services for those interested in reducing drug use

Materials Distributed

Materials included in kit

- Two (2) pre-filled luer-lok syringes with 2 mL of naloxone hydrochloride (1mg/mL)
- One (1) nasal adaptor for luer-lok syringe
- Pamphlet on rescue breathing
- Pamphlet on naloxone administration
- Local options for substance abuse/dependence treatment

Are there groups who opposed to the program and why?

In other states and countries where prescription naloxone programs have been implemented, there has been little organized formal opposition. Detractors consistently have not been able to provide evidence of their claims in the face the evidence showing efficacy. Opposition also tends to be muted because the contrary position (that it would have been better for the victim to die) is untenable. However, there are challenging questions that should be raised and addressed in the interest of providing sound and ethical services; these limitations are addressed in this and following sections of this document.

Media reports have quoted ex-addicts in opposition to prescription naloxone programs. Their concerns center on the positions that empowering drug abusers to administer naloxone will decrease motivation to reduce consumption and increase the likelihood of taking greater risks, and have been echoed by academic researchers (McGregor, Darke et al. 1998). These attitudes are not supported by evidence or experience, and do not reflect the views of all recovering addicts, or even a substantial portion of them (Dettmer, Saunders et al. 2001; Galea, Nandi et al. 2006; Maxwell, Bigg et al. 2006). Evaluation studies of prescription naloxone programs reveal a more complex reality in which the severely negative experience of overdosing can be a wake-up call for change, and, empowerment may encourage altruism and the opportunity to discuss options for reducing consumption. One thing is certain: dead addicts never recover. The DSM-IV criteria for drug dependence include “recurrent substance use in situations in which it is physically hazardous.” In defining substance use disorders, the medical standard acknowledges that poisonings are part of the natural course of these diseases and that *repeated* physical harm is a characteristic of the disorders; interventions aimed at preventing mortality associated with substance use, such as prescription naloxone, do not aim to change the trajectory of substance use progression, but rather are intended to ensure that the individual is alive long enough to realize the future goal of recovery from substance abuse/dependence.

Another criticism of prescription naloxone programs is that if an overdose victim does not go to an ED for treatment, an opportunity for offering drug treatment programs may have been lost. The experience from the field suggests that this opportunity is not currently taken anyways. Of IDUs who were attended by an ambulance in response to their most recent overdose, 82.7% said they did not receive information about drug treatment (Pollini, McCall et al. 2006). Similarly, 73.8% of IDUs who visited an emergency department did not receive drug treatment information from ED staff, and 56.8% of hospitalized IDUs denied receiving drug treatment information from hospital staff. The prescription naloxone program provides a forum for presenting information on substance abuse/dependence treatment programs. This information is part of the initial education when naloxone is prescribed, and the message can also be reiterated when a revived individual returns to the clinical setting for another naloxone prescription. Project Lazarus functions in the context of broader interventions for reduction accidental poisonings in Wilkes County. Discussion of overdose prevention in clinical settings will be promoted through multiple mechanisms, including the prescription naloxone program (details available upon request).

By our approval/allowing this program to go forward are we abetting illicit drug use?

The premise of this question is that by protecting addicts from the negative consequences of their behavior, prescription naloxone wrongly reduces the disincentives to use drugs. The implicit calculus here is that drug use is somehow worse than death, disease, or injury, such that keeping fatal overdose or brain damage as disincentives is a legitimate, even moral, tactic.

[Having naloxone] doesn't influence me to do more; it actually influences me to do less . . . knowing that if they go out I could help them.

From a program participant in Chicago
Maxwell S, et al. J Addict Dis. 2006;25(3):89-96.

If a drug user refuses to get clean and incurs such harm, it is deserved and the example might deter others. However, there is no evidence to suggest that the fear of overdose itself is a deterrent for drug users in withdrawal to not use. Placing blame solely on the addict justifies punitive or *laissez faire* policies on substance use and addiction, and does not fit with the medical field's understanding of substance dependence. (Modified from Clark 2003)

The following evidence serves as a reminder that an overdose is a traumatic event which is likely to induce remorse and self-reflection on a potentially destructive behavior.

Pilot results from the prescription naloxone program in San Francisco found that the six months following training in naloxone administration, participants had a statistically significant *decrease* in injection frequency and a non-significant *increase* in participants entering treatment (Seal, Thawley et al. 2005; Maxwell, Bigg et al. 2006).

In a study of injection drug users, 40.7% of IDUs reported that someone talked to them about drug treatment following their most recent overdose (Pollini, McCall et al. 2006). Drug treatment discussions occurred most frequently with family members (53.7%) and friends (41.6%). In this study, 26.2% sought drug treatment in the 30 days following their last overdose. Of the 149 IDUs who reported talking to someone about drug treatment, 67 (45.0%) subsequently sought treatment.

Therefore, prescription naloxone programs may serve as a platform to engage substance users to address concerns about their consumption, and provide referrals to treatment services.

Are there unintended deleterious effects of approval?

Adverse Events Associated with Administration of Naloxone

To predict adverse events associated with pre-hospital administration of an opioid antagonist, we turn to a study of 1192 naloxone administrations by EMS in a study from Oslo, Norway (Buajordet, Naess et al. 2004). The adverse events reported were mostly related to withdrawal symptoms: confusion (32%), headache (22%), nausea/emesis (9%), aggressiveness (8%), tachycardia (6%), shivering (5%), seizures (4%), sweating (3%), tremor (1%) and miscellaneous (9%). Of note, 3.6% of patients administered naloxone by EMS did not respond satisfactorily to naloxone and were transported to a hospital.

In six of 453 patients treated with emergency naloxone in a hospital in Switzerland, severe or life-threatening reactions occurred 1.3% (95% CI: 0.4%-3%) of patients (Osterwalder 1996). The author predicted that in a sample of 1,000 subjects clinically diagnosed as intoxicated with heroin or heroin mixtures and treated with naloxone, 4-30 complications could be expected. However, subsequent researchers thought that the hazards were overstated in this paper (Hsu, Rao et al. 1997). Despite the lack of strong clinical data on the rate of complications, there is likely to be a background level of poisoning incidents that are recalcitrant to reviving using naloxone. This must be considered in design and evaluation of a prescription naloxone program.

I've saved three people's lives . . . each time that I've helped someone out it's touched me somehow. I start crying because I think, that could've been me, you know, if I was still on the heroin.

From program participant in Chicago
Maxwell S, et al. J Addict Dis. 2006;25(3):89-96.

In a review of 230 peer naloxone administrations in San Francisco, the most common reported adverse events were (in order of frequency): irritability/anger, nausea/vomiting, paramedic harassment, police harassment, and one or two reports of seizure (Personal Communication, Emalie Huriaux, April 2007).

From the FDA approved label for naloxone: “Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures and cardiac arrest. In postoperative patients, larger than necessary doses of naloxone hydrochloride may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of naloxone postoperatively.”

Return of Respiratory Depression

One concern with pre-hospital administration of naloxone is the return of respiratory depression. Three studies have examined this question among those who were administered naloxone by EMS and refused transport to hospital; this is the most analogous situation to prescription naloxone programs for which we have data.

During a five year period in San Diego, 998 out-of-hospital patients received naloxone from EMS and refused transport, against medical advice. A review of medical examiner records found no instances of these individuals dying of opioid poisoning within the 12 hours following naloxone administration (Vilke, Buchanan et al. 1999; Vilke, Sloane et al. 2003).

Similar results were observed among those treated with naloxone by EMS in Finland (Boyd, Kuisma et al. 2006).

“Allowing presumed heroin overdose patients to sign out after pre-hospital care with naloxone is safe. If transported to an ED, a 1-h observation period after naloxone administration seems to be adequate for recurrent heroin toxicity.”

In a study of 573 opioid (predominately heroin) poisoning ED patients in Vancouver, the vast majority of patients were discharged in less than 4 hours (Etherington, Christenson et al. 2000). Only 16% were admitted; the most common additional treatments were supplemental oxygen (13%), repeated dose of naloxone (9%), intravenous antibiotics (2%), assisted ventilations (2%) and fluid bolus for hypotension (2%). This emphasizes the need for informal caregivers to contact emergency medical services.

Program Concerns

It should be noted that there are individuals who have a pattern of substance use that may lead to difficult-to-reverse respiratory depression. Qualitatively, these users seem to be heavy opioid users, who also have used benzodiazepines and alcohol, who have consumed the substances continually over days. Naloxone, administered by either peers or EMS, may not be sufficient to reverse respiratory depression. Rescue breathing may help keep the victim alive until medical attention is received, but, we should recognize that there are documented situations in which pharmacological intervention with naloxone is not sufficient to prevent fatality from poisoning by multiple CNS depressants.

*Life is precious.
I hope to God I'm never on it again,
but if I do relapse I hope someone has
it [naloxone] on them to save my life.
Life is definitely precious.*

From program participant in Chicago
Maxwell S, et al. J Addict Dis. 2006;25(3):89-96.

One potential concern in Wilkes County is the involvement of controlled-release opioid formulations and methadone. Directors of major prescription naloxone programs and academics evaluating them in the United States were queried about their experiences with methadone poisonings in April 2007. Their collective observation was that, even with methadone, single doses of naloxone were sufficient to reverse respiratory depression, and that repeated doses were required exceptionally rarely. (Personal communication: Dan Bigg, Dr. Alex Kral, Dr. Susan Sherman, Dr. Sharon Stancliff, Emalie Huriaux; April 2007).

This may seem odd, given that naloxone has a half-life of 1 to 1.5 hours, which is much shorter than that for methadone (24-30 hours). However, fatal respiratory depression appears to be avoided by single dose administrations of naloxone by peers. While the higher dose may result in greater risk for opioid withdrawal, it may have additional pharmacodynamic benefit, explaining the observed efficacy of prescription naloxone in practice. Clinical experience with intranasal butorphanol (a non-controlled synthetic opioid marketed as Stadol®) revealed longer than expected peak blood concentration levels associated with intranasal administration compared to intravenous administration (Shyu, Pittman et al. 1993). Delayed release of naloxone from nasal mucosa, in addition to not having to undergo first-pass metabolism, may aid in sustained mu-opioid receptor blockade by naloxone when administered intranasally. Out of an abundance of caution, prescription naloxone programs provide two doses of naloxone in each kit, and participants are stressed the importance of staying with the victim to monitor for the return of respiratory depression, as well as the importance of calling 911. We will follow these precautions in Wilkes County.

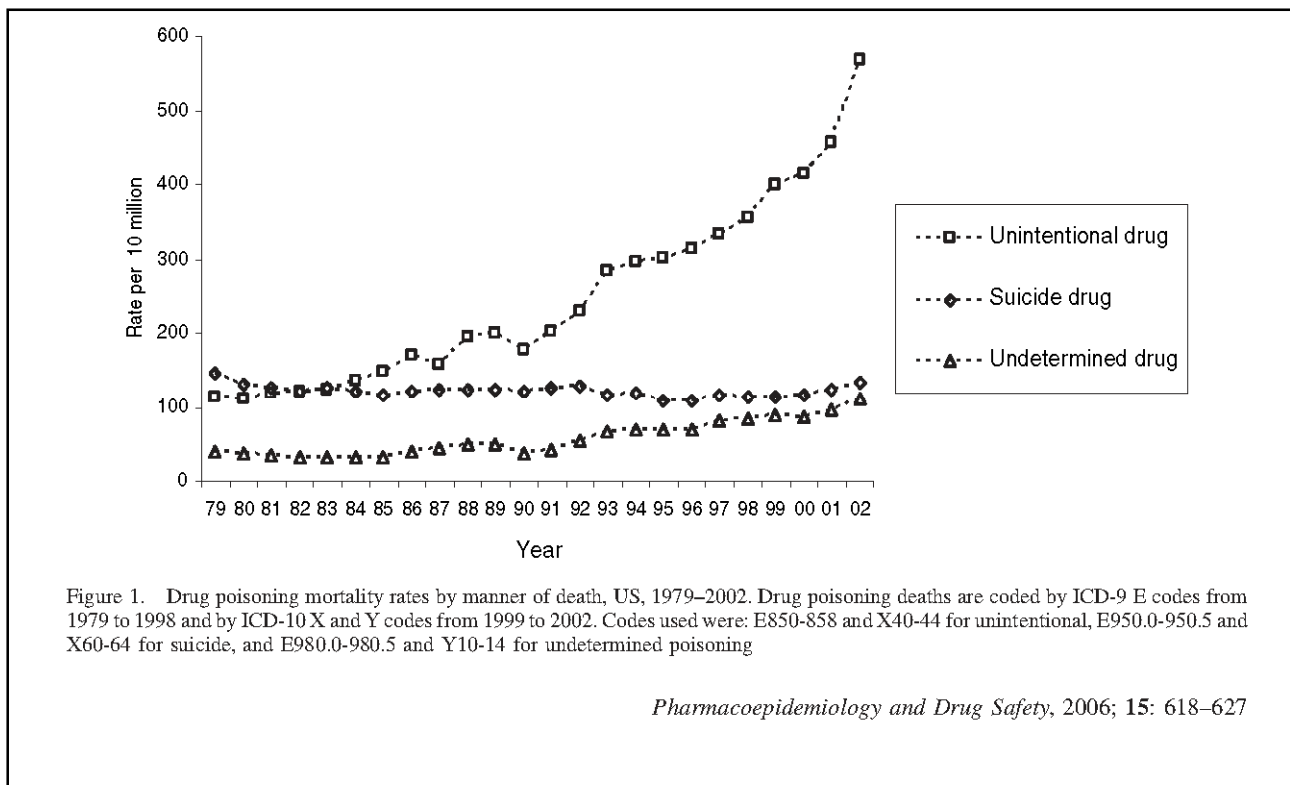
What is the narcotic overdose rate for NC and/or the proposed service area? How many lives/hospitalizations would be saved by this program?

Wilkes County has nearly five times the national rate for accidental opioid poisoning deaths, and three times higher than the state average. The rate of accidental opioid poisoning in the United States was 7.5 per 100,000 per year (2003); in North Carolina it was 10 per 100,000 (2005) (Dasgupta, Brownstein et al. 2007). As a state, North Carolina ranks in the top 10 for methadone poisoning mortality (Dasgupta, Brownstein et al. 2006). National increases in prescription opioid poisoning deaths since the early 1990s have been well documented (Paulozzi 2006; Paulozzi, Budnitz et al. 2006); Figure 1 shows this increase in graphical terms. Wilkes County has three times the state average accidental poisoning deaths, with rates of 27.4 per 100,000 in 2005 and 30.5 per 100,000 in 2006. This year the rates have been similar, with 13 accidental opioid poisoning deaths in Wilkes County, with 2 pending investigations.

In Wilkes County, and in much of North Carolina outside of the largest cities, the primary concern with opioid poisonings revolves around prescription medications, and not heroin. In 2006, there were 26 deaths from unintentional narcotic overdoses in Wilkes County: 8 deaths from prescription opioids (excluding methadone), 12 from methadone, and 6 from cocaine. This mirrors national trends of the increase in prescription opioid poisoning (Paulozzi and Ryan 2006; Centers for Disease Control and Prevention 2007). Prescription opioids most commonly mentioned in North Carolina poisoning deaths are: methadone, hydrocodone, oxycodone and fentanyl. The methadone implicated in opioid poisonings in the state is usually a solid oral formulation, suggesting that the source of diversion is not primarily methadone maintenance programs for opioid dependence. Also, the number of individuals filling prescriptions for methadone for pain management is much larger than the number of patients in methadone maintenance

programs. Staff of the ED at Wilkes Regional Medical Center estimate that a quarter of the opioid poisoning cases involved injection drug use, although this figure was only intended to be an impression, and was not based on systematic data analysis. Opioid-related mortality in Wilkes County does not appear to be due to batches of fentanyl-mixed heroin that caused national concern in 2006.

A recent study of the causes of mortality among released prisoners in North Carolina revealed that between 1980 and 2005, deaths caused by alcohol or other drugs accounted for 11.6% of the mortality among released prisoner (including suicides, unintentional poisonings, mental health disorders and hepatic disease) (Rosen 2007). When compared to the general North Carolina population, released prisoners were much more likely to die from a drug overdose; the standardized mortality ratio for drug poisonings were 8.82 (95% CI: 8.09, 9.60) for whites, and 2.11 (1.84, 2.42) for blacks.



Cost Effectiveness of Prescription Naloxone

In 2005, inpatient hospitalizations for accidental prescription opioid poisoning in North Carolina cost approximately \$20 million of direct hospital charges. About half of this cost was among patients who were uninsured or reimbursed via Medicaid. These figures do not reflect costs for those discharged from emergency departments, transport to hospital, expenditures from emergency medical services and lost productivity.

Project Lazarus is funded through a grant from the Drug Policy Alliance. Additional support in materials and logistics is provided by the North Carolina Harm Reduction Coalition and the Northwest Community

Care Network. The material cost of one intranasal naloxone kit is approximately \$30, which includes two doses of naloxone. Our initial budget of approximately \$8,000 allows for 250 kits to be distributed; if the response is positive, we will try to find other sources of funding for expanding the project.

- Mean cost of inpatient hospitalization for accidental prescription opioid poisoning: \$12,379 (NC) (Agency for Healthcare Research and Quality (AHRQ) 2007)
- Weighted average cost of any hospital admission for poisoning (ED and inpatient): \$1,764 (USA) (Corso, Finkelstein et al. 2006)
- Loss of productivity due to poisoning: \$18,704 (USA) (Corso, Finkelstein et al. 2006)

If a single hospital encounter were prevented, a savings of \$20,468 to \$31,083 would be realized in Wilkes County, including prevention of productivity loss. While preliminary, this suggests considerable potential for the cost-effectiveness of Project Lazarus.

Legal Status of Prescription Naloxone Programs in North Carolina

A review of North Carolina statutes applicable to prescription naloxone programs was conducted by Scott Burris at the Beasley School of Law, Temple University. His complete memorandum, including citations of North Carolina statutes and case law, has been submitted to the Medical Board (Burris 2007). The summary points from his analysis are presented below:

1. Naloxone is not a controlled substance as defined by federal or state law, but is a prescription drug subject to the general laws and regulations that govern all prescriptions in regular medical practice.
2. Prescribing naloxone to opioid drug users (ODU) in this state is fully consistent with state and federal laws regulating drug prescribing.
3. Teaching overdose response techniques, including the administration of naloxone, to naloxone recipients and others who might be in a position to administer it to an ODU to whom it has been prescribed is legal and appropriate.
4. Naloxone may not be given to patients or participants in an overdose prevention program with the explicit purpose of encouraging them to distribute or administer the drug to other ODUs who are not patients.
5. Any legal risks in distributing naloxone in this state are not substantial and can be mitigated by informed program design; the risks of malpractice liability are consistent with those generally associated with providing healthcare, and can be further minimized by following the guidelines we describe.

Legislative Actions to Improve Service Delivery

The following law changes have been passed in states with serious opioid poisoning problems to save lives by providing better services to accidental poisoning victims.

- Absolve practitioners of liability if naloxone is used for someone other than to whom it was prescribed.
- Enact “Good Samaritan” law that prevents prosecution of witnesses who call emergency medical services for family/colleagues of overdose victims.
- Reduce regulatory record keeping requirements for medical encounter and dispensing to allow prescription naloxone programs greater penetration among nonmedical users of opioids.

Additional Information that may be of Relevance

Most injection drug users (IDUs) (69.7%) reported ever witnessing an overdose (Pollini, McCall et al. 2006). The most common responses were walking the victim around (70.8%), shaking them (64.9%), and inflicting pain (62.6%). One in four (25.8%) injected the victim with salt water. Two thirds (63.4%) called 911, but more than half delayed the call by 5 or more minutes. The most common reason cited for delaying or foregoing the 911 call was the belief that they could revive the victim themselves, followed by fear of police involvement.

From a study of injection drug users, we know that the vast majority of IDUs were in the company of others at the time of their last overdose (Pollini, McCall et al. 2006). More than half (58.5%) were with a friend or acquaintance, 13.7% with a family member and 12.3% with a spouse or partner; however, 18.0% reported overdosing while alone. This suggests that education on the use of naloxone should be expanded to more than the at-risk individual. This could be achieved through a broad educational campaign and providing simple written and illustrated instructions with the naloxone kits. However, convincing colleagues of drug users to come in for training will be a challenge; therefore a non-stigmatizing and broad based public health approach is needed.

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