

Intranasal Naloxone for At-Home Opioid Rescue



Tens of thousands of lives could be saved from accidental opioid overdose deaths if naloxone were more widely available and opioid users, caregivers, and first responders were trained in its use.

By Stewart B. Leavitt, MA, PhD

Naloxone is a well-tested antidote for reversing often-fatal respiratory depression due to opioid overdose poisoning. So, the prescription of naloxone for at-home intranasal administration, along with complete instructions for its emergency use, may be the best antidote for stemming rising rates of prescription-opioid overdoses and fatalities in the United States population. Yet, there are some major obstacles to be overcome.

The Rx-Opioid Overdose Crisis

The annual incidence of opioid-overdose-associated mortality on a nationwide scale has been difficult to assess due to incomplete reporting systems, inadequate forensic determinations at autopsy, and other factors. According to the 2007 Annual Report of the American Association of Poison Control Centers, analgesics of all types were the most frequently involved agents in human-exposure calls for help (about 312,000 calls), and opioids were the second most frequently associated with fatalities; coming

after sedatives, hypnotics, and antipsychotic agents.¹

Data from the U.S. Centers for Disease Control indicate that accidental drug overdose deaths nationwide escalated by more than 800% between 1980 and 2005 — in 2005 there were about 22,500 accidental drug overdose fatalities² and 8,541 deaths were associated specifically with prescription-opioid analgesics.³ Another report, from the National Center for Health Statistics, notes that from 1999 through 2006, the number of fatal poisonings involving opioid analgesics more than tripled, rising from 4,000 to 13,800 deaths. Opioid analgesics were involved in nearly 40% of all poisoning deaths in 2006, with persons aged 35 to 54 years at greatest risk.⁴ While the data vary somewhat depending on the source, today's opioid overdose crisis clearly touches the lives of a great many American individuals and families, regardless of age, social class, ethnicity, or gender.

Individual states have reported data reflecting increasing concerns about opioid-related overdose fatalities. For

example, in 2006, there were 275 opioid-involved fatalities in West Virginia representing 93.2% of all deaths attributed to pharmaceuticals in that state.⁵ In 2007, 2,328 people in Florida died from accidental opioid-analgesic overdose.⁶ Also in 2007, there were 637 opioid overdose fatalities in Massachusetts, surpassing motor vehicle injury deaths.⁷

Similarly, alarming reports have come from Maine, North Carolina, Tennessee, Washington, Ohio, and other states. In 2006, Utah, New Mexico, Louisiana, Kentucky, Oklahoma, West Virginia, and Nevada had the highest rates of opioid-analgesic-related fatalities in the United States, ranging from 14.2 to 19.4 per 100,000 population compared to a national average of 9.14.^{4,8} Reported opioid overdoses may be associated with the misuse or diversion of opioid analgesics as well as with illicit street drugs like heroin; however, most accidental opioid overdose fatalities today are linked to prescribed opioid analgesics.²

Life-threatening opioid overdose takes place over time—it is not a sudden cata-

strophic event—it usually occurs while other persons are present or in the vicinity and it can be averted with proper monitoring and care.^{8,9} In one investigation of opioid-related deaths, the majority of fatalities (65%) occurred within one week of a change in medication dose and most decedents were discovered in the morning at home in bed.¹⁰ In most cases, other persons were likely present in the home and might have saved the victim had they been armed with proper knowledge and an antidote.

The Naloxone Solution

Fortunately, there is an antidote that acts rapidly, effectively, and safely—naloxone. This agent was FDA-approved in 1971 and has been used for decades by emergency medical services (EMS) personnel for reversing opioid overdose and reviving victims who otherwise would have died. Naloxone is an opioid antagonist, meaning that it temporarily displaces opioids from their receptors in the brain and protects the person for a period of time from further action by the opioids.

Naloxone is an unscheduled drug with no abuse potential and a very favorable safety profile. On rare occasions, nausea, vomiting, hypertension, pulmonary edema, tachycardia, or arrhythmia have been reported following naloxone administration^{11,12}; however, it is often unclear whether such effects were due to naloxone, the ingested opioid and/or other drugs, or the victim's prior physical condition. The only contraindication is hypersensitivity to naloxone or any component of the formulation.¹³ If administered to a person who has not taken opioids, naloxone simply has no pharmacological effect and naloxone itself has no overdose potential.^{2,14}

Besides its use by EMS teams worldwide, some harm-reduction organizations—starting in Europe, then in Australia, England, and the United States—have provided prescription naloxone directly to addicted intravenous-drug users (IVDUs; most often heroin users). To help curtail opioid overdose deaths, these individuals have been provided training in recognizing overdose, basic life-support techniques (e.g., rescue breathing, recovery position, etc.), and how to administer naloxone. Participants are typically provided a container of naloxone and one or more needle-tipped syringes for intramuscular injection of the

drug. They are encouraged to share this information with drug-using peers so they can assist each other during an overdose emergency.

To date, naloxone-distribution programs focusing on IVDUs have been initiated in 17 states and several cities (New York, Baltimore, Boston, San Francisco, and Chicago).¹⁵ Although these programs were somewhat controversial at first, successes have been well-documented. According to one report, as of 2007 a program started in Chicago in 1998 had trained and distributed naloxone to 10,211 participants resulting in 1,011 documented episodes of life-saving overdose reversal with naloxone.²

Overall, as of 2008 in the U.S., about 21,000 persons at risk were trained on rescue naloxone and 2,600 overdose reversals were reported⁹—more than a 10% return in lives saved by the investment in naloxone training and distribution. A study by the Overdose Prevention and Reversal Program at the Lower East Side Harm Reduction Center in New York City concluded that naloxone is “undeniably advantageous for individuals to effectively revive an overdosing friend or family member, instead of resorting to potentially harmful and less effective methods of resuscitation.”²²

Some European countries are promoting increasingly unrestricted naloxone access for more effective overdose prevention. The United Kingdom added naloxone to its list of emergency medications—such as adrenaline and glucagons—that may be administered by anyone in a life-saving situation and has initiated community-based naloxone distribution programs.¹⁶ Naloxone has been available over-the-counter in Italy since 1998,⁹ and advocates in the United States have suggested the drug should be changed from prescription-only to OTC status.²

Research from Yale University in 2008 demonstrated that, with minimal training, any individual can learn to recognize and effectively respond with naloxone to an opioid overdose emergency just as effectively as medical professionals.² Some programs have found that no more than 10 minutes of instruction is required.¹⁷ Clinical trials have found extremely high rates of retention of lessons learned during naloxone-administration training, and many patients took it upon themselves to train family member or friends in its proper use.^{18,19} It should be empha-

sized that most harm reduction programs incorporating naloxone have involved actively addicted IVDUs, a population of individuals typified by low levels of reliability and motivation; therefore, the responsible behaviors of participants and successes of these programs are all the more noteworthy.

Intranasal Naloxone Can Benefit Patients with Pain

Naloxone is most commonly administered via intramuscular (IM) or intravenous (IV) injection, but it also can be administered subcutaneously, or intranasally using an atomizer device that delivers a mist of naloxone to nasal mucus membranes. Whereas the filling of needle-tipped syringes and their use by IVDUs poses few problems, the use of needleless intranasal methods would be more appealing to, and safe for, the general population of patients with pain and their caregivers.

Administration of naloxone intranasally is an off-label application of the drug, but is in use by EMS responders in Utah and New Mexico, as well as other states, and within community settings by overdose prevention groups in Massachusetts and New Mexico.² Research studies attesting to the safety, convenience, and effectiveness of intranasal drug delivery have been widely reported in the literature.^{20,21} Furthermore, a series of clinical studies has demonstrated that intranasal naloxone avoids potentially dangerous needlesticks and the risk of air embolism while maintaining potency and efficacy for reversing respiratory depression due to opioid overdose.²² Ongoing research and evaluations of this have been recommended.^{14,23}

There is a website run by independent academics and healthcare professionals solely dedicated to raising the awareness and profile of the use of take-home naloxone as a mechanism for reducing opioid-related deaths worldwide.²⁴ Perhaps the most significant demonstration in the U.S. of take-home intranasal naloxone for opioid overdose rescue in the community has been taking place in Wilkes County, North Carolina.

Called Project Lazarus, the initiative was approved in 2007 to stem the rising rate of opioid-analgesic overdose among patients being treated for pain. It is an opioid overdose rescue program embedded within a healthcare provider and

Table 1. Groups of Patients Who May Be at Risk of Overmedication or Overdose
<p>The following groups of patients have been identified as potentially benefiting from having lifesaving naloxone on hand, along with proper education in its use, to deal with an opioid overmedication or overdose crisis:</p>
<ul style="list-style-type: none"> <input type="checkbox"/> Any patient receiving a prescription for a higher-dose (>50 mg of morphine equivalent/day) of an opioid or for the longer-term management of chronic cancer or noncancer pain. <input type="checkbox"/> Patients being rotated from one opioid to another, when there may be incomplete cross tolerance. <input type="checkbox"/> Any methadone analgesia prescription to an opioid naïve patient, or for a patient rotated from another opioid to methadone. <input type="checkbox"/> Patients released after emergency medical care involving opioid intoxication or poisoning. <input type="checkbox"/> High-risk patients with suspected history of substance abuse, dependence, or nonmedical opioid use.
<p>Opioid prescription for patients having any of the following...</p>
<ul style="list-style-type: none"> <input type="checkbox"/> Smoking, COPD, emphysema, asthma, sleep apnea, respiratory infection, or other respiratory illness or potential obstruction. <input type="checkbox"/> Renal dysfunction, hepatic disease (including hepatitis), cardiac illness, HIV/AIDS. <input type="checkbox"/> Known or suspected concurrent heavy alcohol use. <input type="checkbox"/> Concurrent benzodiazepine or other sedative prescription. <input type="checkbox"/> Concurrent antidepressant prescription. <input type="checkbox"/> Patients who may have difficulty accessing emergency medical services (distance, remoteness). <input type="checkbox"/> Voluntary request from patient or caregiver.
<p>Additionally, the following special populations would benefit...</p>
<ul style="list-style-type: none"> <input type="checkbox"/> Patients participating in methadone or buprenorphine detox/maintenance programs (for addiction); especially during the start-up induction period or during "interim methadone maintenance." <input type="checkbox"/> Patients recently released from opioid detoxification or mandatory abstinence programs (with no opioid tolerance and a potential for opioid relapse). <input type="checkbox"/> Prior opioid abusers being released from incarceration (with no opioid tolerance and risk of relapse).

community education program for proper opioid use and misuse prevention (and is similar in principle to the newer patient/caregiver education program, Opioids911-Safety).²⁵ The Project Lazarus protocol goes a step further, asking healthcare providers in the area prescribing opioid analgesics to also prescribe intranasal naloxone (for pickup at a local pharmacy) to a broad range of patients who may be at risk of overmedication or overdose (see Table 1).^{2,9,14,26}

According to the Drug Policy Alliance, "support is growing among some physicians and other health professionals for regularly pairing naloxone with all opioid prescriptions. Under this scenario, physicians would routinely write a prescription for naloxone to accompany every prescription for opioid medications. Such a convention would have the dual benefits of safeguarding the life of the patient and normalizing naloxone by educating the greater public about its function and proper use."² And it also must be recognized that, besides potentially rescuing the patient for whom opioids were prescribed, intranasal naloxone could be a lifesaving measure for family members or others (even household pets) who inadvertently or intentionally consume the patient's opioid medication and experience an opioid intoxication or poisoning crisis.¹⁴

Cost of take-home naloxone should not be a prohibitive factor. The material cost of the intranasal naloxone kit available as part of Project Lazarus is estimated at about \$25, including two prefilled naloxone syringes and an atomizer tip.⁹ The naloxone component probably would remain viable for several years and the syringes and atomizer tip are nonperishable items. The prescribing of intranasal naloxone for at-home administration typically specifies two prefilled needleless syringes (each 2 mL [1 mg/mL], Luer lock taper) with an atomizer tip attachment (Luer lock connection). A logistical challenge at present is that, while the two items are available separately from different pharmacy supply sources, they are not typically stocked as a kit by community pharmacies; therefore, strategies for achieving easy access need to be considered.

Another appropriate naloxone-delivery system for use by patients and caregivers might be an Autoinjector (e.g., similar to the EpiPen®) for easy and safe

IM administration. However, such a device is not available and manufacturers have expressed no interest in its development.

Concerns Unfounded, Yet Obstacles Remain

Past concerns about expanding access to naloxone in the general population have centered on potential unintended consequences of encouraging risky behaviors by opioid consumers, such as (a) recklessly using larger opioid doses since an antidote is at hand, (b) failing to seek timely medical attention in the event of an emergency, or (c) ingesting additional opioids after naloxone administration to counter its effects. However, the many research projects to date investigating these issues have unanimously demonstrated that such concerns are unfounded.² Furthermore, it has been stressed that, just as lay family members, friends, or other caregivers can be trusted to administer epinephrine to reverse anaphylactic shock, naloxone can be used to avert opioid poisoning fatalities in the community.^{8,9}

Another concern might be legal issues surrounding naloxone prescription and distribution in the U.S. The report of a special project at the Temple University School of Law examining such concerns noted that naloxone is not a controlled substance as defined by federal or state laws, and the drug may be prescribed by physicians in every state (almost all states also allow advanced practice nurses [APNs] and physician assistants [PAs] to prescribe naloxone).²⁷ Furthermore, almost all states allow physicians, and APNs/PAs in many cases, to directly dispense naloxone without restrictions, and the remainder allow dispensing with minor restrictions. And, it is deemed legal and appropriate in all states to teach overdose response and naloxone administration techniques to persons receiving a prescription for naloxone and others who might be in a position to administer it in an emergency.

Despite these findings, some healthcare providers might be concerned about prescribing and possibly distributing naloxone because of legal liability concerns. Several reviews of existing law have concluded that prescribing naloxone and providing proper training in its use does not expose physicians to unusual risks of medical liability as long as the physician acts (1) in good faith, (2) in the course of

professional practice, and (3) for a legitimate medical purpose.^{2,27}

Experts generally agree that any medical liability can be reduced by ensuring that those who are given a naloxone prescription understand how it works and are instructed in its proper use. They also point to the routine practice of making available lifesaving medications—such as glucagon for diabetes or epinephrine for anaphylaxis (both of which have greater adverse reaction potential than naloxone)—to third parties (caregivers, family, friends) for emergency administration. And, the experts note that there is wide latitude in federal law for the prescription

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of drugs for applications beyond those indicated on their labels, which would be the case with *intranasally-administered* naloxone.^{2,28} Finally, most of the past concerns have centered on the prescribing of naloxone with needle-tipped syringes to actively-addicted intravenous-drug users (IVDUs), which is not relevant to intranasal naloxone for patients with pain who are legitimately prescribed opioid analgesics.

Still, there are two current and seemingly insurmountable obstacles blocking intranasal naloxone for at-home opioid rescue. First, there is no widespread distribution of prefilled naloxone syringes and atomizer tips; in fact, there does not even appear to be a single mail-order source where both items can be purchased together. Therefore, today, a qualified healthcare provider cannot simply write an intranasal naloxone prescription for delivery at a local pharmacy along with the patient's opioid prescription. Second, U.S. government agencies have not shown any interest in intranasal naloxone as a risk-mitigation strategy having robust potential for countering rising concerns about prescription-opioid overdoses and deaths. Reasons for such disinterest are unclear and baffling; and further, perhaps as a consequence, manufacturers and distributors also have not shown any inter-

est in pursuing the marketing of a take-home intranasal naloxone kit.

Conclusion

As Jill Harris, Managing Director of Public Policy at the Drug Policy Alliance, has noted: “Tens of thousands of lives could be saved if naloxone were more widely available and more people (including doctors, pharmacists and other healthcare professionals, as well as law enforcement professionals many of whom are currently unfamiliar with naloxone), were trained in its use. Providing take-home naloxone to opioid users, along with instructions for its use, could signif-

icantly reduce the number of accidental overdose deaths.”²⁹

Yet, probably nothing will be done on a nationwide scale to make this antidote more readily accessible until healthcare professionals, their patients, and relevant stakeholder organizations recognize the life-saving potential of intranasal naloxone and demand its availability. ■

Disclosure

The author has no financial interests in or any relationships with manufacturers, distributors, or marketers of naloxone products.

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