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Expanded Access to Naloxone: Options for Critical Response to the Epidemic of Opioid Overdose Mortality

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The United States is in the midst of a prolonged and growing epidemic of accidental and preventable deaths associated with overdoses of licit and illicit opioids. For more than 3 decades, naloxone has been used by emergency medical personnel to pharmacologically reverse overdoses. The peers or family members of overdose victims, however, are most often the actual first responders and are best positioned to intervene within an hour of the onset of overdose symptoms.

Data from recent pilot programs demonstrate that lay persons are consistently successful in safely administering naloxone and reversing opioid overdose. Current evidence supports the extensive scaleup of access to naloxone. We present advantages and limitations associated with a range of possible policy and program responses. (*Am J Public Health*. 2009;99:402–407. doi:10.2105/AJPH.2008.136937)

RAPID INCREASES IN DEATHS

from heroin-related overdose began in the 1990s, as average mortality per 100 000 population in 25 US cities increased from 8.7 in 1988 to 13.8 in 1997.¹

By 2004, poisoning was the second leading cause of death from unintentional injury in the United States.² Nearly all such deaths were attributed to illicit and prescription drugs,² fueled by a dramatic rise in the incidence of opioid-involved overdose, which paralleled similar increases in Denmark, Finland, Iceland, Norway, Sweden, Spain, Italy, Austria, Australia, England, and Wales.^{3–5}

Fatal overdose is the leading cause of death among those who misuse illicit drugs, exceeding mortality from AIDS, hepatitis, or homicide.⁶ In a 33-year longitudinal study in California, 581 opiate-dependent participants had experienced an average of 18.3 years of potential life lost before age 65,⁷ with heroin overdose

accounting for the largest proportionate mortality (22.3%). The years of potential life lost for this group was 6 times greater than in the general US population.

Although heroin-related overdose deaths have continued to rise, recently there has been an alarming increase in mortality from drug overdose associated with the misuse of prescription opioid analgesics. Data from the National Vital Statistics System indicate that the recent 62.5% increase in deaths from unintentional poisoning—from 12 186 in 1999 to 20 950 in 2004—was primarily attributable to increased misuse of prescription opioid analgesics.² According to mortality data on multiple causes of death from the National Center for Health Statistics, the number of opioid analgesic poisonings listed on death certificates increased 91.2% between 1999 and 2002; in the latter year, it accounted for 5528 deaths, more than those

associated with either heroin or cocaine.⁸

The current US epidemic of opioid-related overdoses is spreading geographically and demographically. Mortality from such overdoses is expanding from urban areas to suburban and rural regions, where overdoses are usually prescription related and general awareness and treatment services are relatively lacking.⁹ Likewise, overdose mortality is on the rise among non-Hispanic Whites, women, adolescents and young adults, and those with a history of chronic pain and depression.^{2,9–12} Methadone, oxycodone, hydrocodone, and fentanyl account for the vast majority of misused prescription opioids.^{10,13} Common sources include not only illicit dealers but friends, relatives, physicians, and emergency departments.¹¹ For instance, in a study in rural southwestern Virginia, about half of the women who died of opioid-related overdose had



prescriptions for the substance as well as a history of chronic pain, depression, or anxiety.¹⁰

FATAL OVERDOSE

Overdose occurs when the opiate binds to the μ_2 receptors in the brain stem, desensitizing it to the carbon dioxide levels in the blood so that breathing mechanisms are not triggered, leading to respiratory failure.^{14,15} This process, however, can be interrupted by introducing naloxone, a safe and effective opiate antagonist that can reverse the effects of a wide range of natural, semisynthetic, and synthetic opioids. Naloxone can be safely administered by intravenous or intramuscular injection, a procedure that requires little skill. More recently, naloxone has also been formulated for intranasal administration, which has been shown to be a safe and generally effective “first line prehospital intervention.”^{16(p223)}

Once administered, naloxone displaces the opiate at the μ_2 receptors, effectively reversing potentially fatal opiate effects within a few minutes.¹⁵ Naloxone, which is an uncontrolled substance, has no potential for abuse or overdose nor does it have any pharmacological activity in the absence of opioids or other opioid antagonists.^{15,17,18} Moreover, emergency room staff and paramedics have routinely used naloxone to reverse opioid overdoses for 3.5 decades without any widely reported safety problems.¹⁹

The efficacy of naloxone is fundamentally time dependent. Death from overdose typically occurs within 1 to 3 hours, although earlier

in some cases, leaving a brief window of opportunity for intervention.^{15,18,20} Between 64.6% and 97.4% of those who misuse drugs have reported witnessing an overdose, with respondents in one study recounting an average of 6 instances.^{1,21–24} Other surveys have reported that 58% to 86% of heroin-related overdoses occur in the company of others.^{4,23,25,26}

Despite the presence of others, timely transportation of victims to emergency departments or contact with first-responder services is inhibited by numerous structural barriers. For those in attendance, calling 911 is often a last resort, occurring only an estimated 10% to 56% of the time,^{14,20,27} because, in the United States, the police are usually notified of a 911 call reporting an overdose and frequently appear at the scene.^{18,22,28} Because many of those who misuse opioids are on parole, have outstanding arrest warrants,^{18,20} or otherwise don't want to be identified, they are understandably disinclined to invite police involvement—a problem reported in numerous countries.¹⁸ In one study, 42% of those who had called 911 because of a heroin overdose reported seeing police accompany the paramedics. Some even reported being searched and interrogated by the police, checked for parole violations and warrants, or treated disrespectfully.¹ Even murder or manslaughter charges are possible if the caller is suspected of supplying the drugs used in a fatal overdose.^{15,27}

Instead, peers (at the scene) often attempt to revive victims themselves, sometimes employing such dubious strategies as

injecting them with salt, milk, or stimulants like cocaine; immersing them in a cold bath; massaging their hearts; or deliberately inflicting pain.^{14,22} Such interventions are generally ineffective and potentially dangerous to the victim, but peers, even those who call 911, almost always first attempt these methods.²⁷ Others may initiate cardiopulmonary resuscitation²² but, because few are adequately trained, their attempts are often unsuccessful.¹ Thus, although peers are often on the scene and willing to help,¹ time can rapidly run out for those in need of urgent intervention.

Compared with heroin users, misusers of prescription opioid analgesics misuse smaller amounts of opioids and report less current and lifetime intravenous drug use, fewer family and social problems, and less income from illegal sources.²⁹ However, their tendency to keep opioid misuse concealed leaves friends and family members ill prepared to identify and respond to an overdose. Such secrecy predisposes adolescents, who most frequently misuse opioid analgesics,³⁰ to accidental death.

In all cases of opioid overdose, it makes intuitive sense to reduce the time it takes to administer naloxone by getting it into the hands of those best positioned to respond rapidly. Indeed, support for this idea among opioid misusers is overwhelming. In a survey of 82 street-recruited drug users in the San Francisco Bay Area, where 89% had witnessed 1 or more heroin overdoses, 87% expressed a strong desire to participate in an overdose management training program in which

they would receive take-home naloxone and training in resuscitation techniques; 91% said they would want peers to administer naloxone to them if they overdosed.¹ A quality-of-life survey in Rhode Island similarly found that 88.5% of drug users were willing to administer naloxone to prevent an overdose fatality.²⁴ A study in London also found that 70% of 142 opiate users in methadone treatment were in favor of naloxone distribution,²¹ and 89% said that they would have administered naloxone at the last overdose they witnessed had they been able. The logic and support for placing time-critical medications in the hands of nonmedical persons is not new. Epinephrine injections are made available as a life-saving measure for people at risk for suffering anaphylaxis, and glucagon injections are provided to diabetes patients in case of severe insulin reactions.

SAFETY, EFFECTIVENESS, AND RISK–BENEFIT RATIO OF NALOXONE

Opposition to proposals that would enable high-risk persons and their peers to access and administer naloxone typically questions the safety of its pharmacological properties and administration procedures, as well as the potential of higher-risk drug use practices. However, the available data suggest that these concerns are not valid, nor, if they were, would they outweigh the potential benefits of increasing access to this emergency intervention.

The first set of objections relates to concerns about the unsafe



administration of naloxone, lack of follow-up care, and the possibility that overdose victims may be subjected to unsafe practices by their peers. One commonly cited safety concern is that drug users will prematurely administer additional opioids to counter the withdrawal effects precipitated by naloxone. In at least 1 study, however, premature reinjection of heroin was not found to be a problem among overdose patients who had signed out of a hospital against medical advice after being revived with naloxone.³¹ Furthermore, the country's largest naloxone distribution program, in Chicago, reports that, since its inception in 2001, drug users who were trained in naloxone administration experienced no difficulties in persuading victims not to reinject more heroin.¹⁷ There are no documented cases of practices or problems associated with the readministration of opioids following naloxone administration.

Naloxone has a shorter half-life than heroin, leading to concerns about the potential recurrence of respiratory depression after the effects of naloxone wear off. On one hand, such situations would simply warrant a second dose of naloxone. On the other hand, of 319 reports of peer administration of naloxone in the Chicago pilot study, not 1 case required a second dose of naloxone to counter a recurrence of overdose symptoms.¹⁷ This is consistent with the reported efficacy of single-dose administration in formal medical settings.¹⁷ There is also apprehension that risk would increase if the companions of someone overdosing were themselves

intoxicated^{32,33}; however, peers already attempt various interventions when naloxone is unavailable. As indicated by the extremely low rates of adverse events in the evaluation of numerous pilot studies of naloxone distribution, drug-using peers are capable of saving lives with naloxone.^{6,17,34,35}

Complications such as seizures and arrhythmia have been reported after naloxone administration on very rare occasions. However, their links to naloxone have been questioned in the medical literature, and, even if there is a connection, it constitutes a risk only for patients with pre-existing heart disease.¹⁵ A 1996 study linking naloxone to asystole, fits, pulmonary edema, and violence is often cited to suggest its pharmacological dangers,³⁶ but these events occurred in just 1.3% of the 453 administrations in that study. Similarly, in a study of 1192 episodes in Norway in which paramedics administered naloxone out of hospital, just 3 adverse events—or 0.25% of cases—were considered serious enough to require hospitalization.³⁷ The same study observed such nonserious side effects as confusion, headache, nausea or vomiting, and aggressiveness in about 45% of cases. These experiences are not adverse events per se, but acute withdrawal symptoms that fade within 1 to 2 hours and do not require hospitalization.

Another objection is that naloxone availability may encourage more frequent or higher-volume drug use by acting as a safety net. However, naloxone precipitates the same unpleasant symptoms that opioid-dependent people are trying to stave off with their opioid

use in the first place, except that, with naloxone, the symptoms are more intense. People who use opioids and who have experienced the acute withdrawal effects that accompany naloxone consistently deny that they are more comfortable using heroin frequently or in higher doses because of naloxone availability.^{6,17,34} Rather, studies suggest that increasing health awareness through training programs that accompany naloxone distribution actually reduces the use of opioids and increases users' desire to seek addiction treatment.^{6,17,38}

Despite the availability of this safe and effective treatment, by and large, US public health institutions have not adequately concerned themselves with the issue of accidental opioid overdose. Only a handful of individual state health departments, researchers, and other organizations that serve people who misuse opioids have begun to take some initiative. On June 25, 2008, the United States Conference of Mayors unanimously called for increased city-coordinated drug prevention efforts, which included measures to expand access to opioid antagonists.³⁹ However, given the size and growth of overdose fatalities in cities and rural communities in the United States, further action to dramatically increase the availability of naloxone for these often hard-to-reach populations is urgently needed. In order to promote discussion about this critical research, policy, and implementation agenda, we describe 3 potential policies for expanding access to naloxone in the following sections. Each option would incorporate appropriate

standardized educational instructions just as existing naloxone distribution programs already do.

PRESCRIPTION NALOXONE

In 1971, the Food and Drug Administration (FDA) determined that access to naloxone required a prescription from an authorized health care provider. Although some physicians may be reluctant to prescribe naloxone to suspected opioid-misusing patients, at least 1 legal analysis, by Burris et al., concluded that health care providers do not act outside state and federal regulations in prescribing naloxone to their at-risk patients¹⁵ and the risks of liability are low and commensurate with those generally associated with providing health care. Recent Good Samaritan laws in states such as Illinois and New York have specifically provided legal protection to physicians for prescribing naloxone and to laypersons for carrying and administering the drug.⁵ The US Conference of Mayors has also expressed strong support for the increased adoption of Good Samaritan immunity policies.³⁹ Encouraging clinicians to prescribe naloxone, as standard practice not only to suspected or reported opioid abusers but also to all patients who receive moderate to high doses of prescription opioids, seems warranted. Project Lazarus, a pilot program for naloxone distribution in North Carolina, for example, describes 13 indications for which health care providers should consider prescribing naloxone.⁴⁰

Very few studies have examined health care providers'



naloxone-prescribing attitudes or practices, but at least 2 suggest that significant efforts to increase awareness about naloxone and overcome negative stereotypes about those who use opioids are desperately needed. In a survey of 327 emergency medical service providers, 56% of respondents did not feel that training drug users to administer naloxone would be effective.⁴¹ Respondents who had worked in emergency medical service longer, however, were more likely to believe that the intervention would be effective. In another study, with a sample (n=571) that was skewed toward physicians with greater awareness of drug use issues, only 23% indicated that they had heard of prescribing naloxone to drug users as a way of preventing fatalities in the event of overdose.³⁸ A slight majority (54%) also indicated that they would never “consider prescribing naloxone and explaining its use to an [intravenous drug-using] patient.”^{38(p130)}

Although pursuing additional legislation, education, and in-service training to expand physicians’ willingness to prescribe naloxone is essential, access to naloxone for those who are either unable or afraid to see physicians or to talk about their drug misuse will remain limited.

NALOXONE DISTRIBUTION PROGRAMS

Measures to expand the number and reach of current naloxone distribution programs may help to improve access to the users of illicit opioids that they typically

serve. Such programs legally distribute naloxone via physician prescriptions to those who are at risk for overdose and are most likely to be available as a first responder in emergency overdose situations. Naloxone has been distributed to those at high risk of overdose in Germany and Britain.³⁵ In the United States, 52 such programs are operating legally in 17 states as of December 2008 (L. Enteen, project manager at DOPE, Harm Reduction Coalition, written communication, December 2008).⁴² Evaluations of pilot distribution programs in Chicago, IL; San Francisco, CA; New York, NY; and Baltimore, MD, have consistently demonstrated positive outcomes.^{6,17,34,35} For instance, since 2001, the Chicago program has distributed over 10 000 vials of naloxone and received over 972 verified reports of successful overdose reversals without any adverse events from naloxone administration (D. Bigg, Director, Chicago Recovery Alliance, written communication, December 2008). Indeed, a recent evaluation of 6 naloxone training and distribution programs showed that trained laypersons were as adept as are medical experts in overdose recognition and treatment at recognizing an opioid overdose and knowing when naloxone use was necessary.⁵

The current reach of these distribution programs is quite limited, because they are usually part of needle exchange programs that predominantly serve persons misusing illicit drugs in urban areas. Unless these programs are dramatically expanded, the vast majority of those misusing opioids will not have access to naloxone.

With political goodwill and sufficient funds, distribution capacity could be significantly increased. Although the US Conference of Mayors has shown support for these programs,³⁹ mustering the resources to benefit people at risk of misusing opioids, a socially unpopular population, will require aggressive political advocacy based on empirical evidence.^{43,44}

FDA RELABELING OF NALOXONE

Given the fundamental limitations of access to physician prescriptions and distribution programs, relabeling naloxone as an over-the-counter drug is an option that merits consideration. Naloxone has been available over-the-counter in Italy since the 1980s without any reported negative consequences.^{15,35} It has no potential for abuse and therefore is not a controlled substance, even in the United States. Its FDA label as a prescription drug, however, triggers state health care provider licensing laws as well as laws against practicing medicine without a license or possession of a prescription drug without a prescription (S. Burris, JD, professor, Temple Law School, Philadelphia, PA; written communication, January 2008).

FDA relabeling of the drug would clear up any legal uncertainties that are currently associated with prescribing to third-party lay nonusers, which is still prohibited except in California, New York, New Mexico, and Connecticut (S. Burris, written communication, January 2008). Greater legal certainty would allow wider availability and

distribution of naloxone and help organizations that serve opioid users to expand overdose prevention services without the burden of obtaining physician prescriptions. Those whose contact with physicians or naloxone distribution programs is limited would have additional access through pharmacies and peer-to-peer networking and distribution. Other potential first responders, such as law enforcement officers or the staff of establishments frequented by those at risk, could also be trained and equipped to provide emergency life-saving care. Evidence also indicates that friends and families of those who use opioids are an overlooked carer population that is in need of training in overdose prevention and reversal.⁴⁵

There are 2 basic forms of naloxone delivery that should be considered by the FDA for over-the-counter labeling. Naloxone is commonly injected—either intravenously, intramuscularly, or subcutaneously—and added risks associated with needles and syringes may pose barriers to relabeling. An alternative is intranasal naloxone. A quick review in 2005 of 8 studies suggested that intranasal naloxone is a safe and effective “first line prehospital intervention.”¹⁶ A recent randomized study of 166 participants confirmed no significant difference between intramuscular and intranasal routes of delivery in terms of mean response time, adequate response, hospitalizations, and minor adverse events.⁴⁶ Officials in Massachusetts and New Mexico, for example, are already distributing intranasal naloxone kits to heroin-dependent



persons to treat potential overdose, and officials in North Carolina have submitted similar proposals to appropriate authorities.^{40,47}

The FDA requires that over-the-counter drugs be generally recognized as safe and effective and not be misbranded.⁴⁸ Evidence showing a low incidence of adverse reactions or of significant side effects, a low potential for harm from abuse, and a reasonable expectation of a clinically significant pharmacological effect would need to be provided. The drug would require proper labeling with written instructions for appropriate use as well. The benefit–risk ratio demonstrated by the existing evidence supports a reasonable case for relabeling naloxone as a nonprescription drug on the basis of these criteria.

Some critics have objected to the lack of robust research on the safety and effectiveness of naloxone in the hands of laypersons.^{36,49} The skill required for naloxone administration is low, and because it cannot be abused and is pharmacologically inactive in the absence of opioids, even unwarranted administration is unlikely to cause adverse reactions. The risk–benefit ratio may be acceptable in light of the high incidence of overdose mortality. Although the FDA ordinarily requires robust evidence produced by controlled trials before relabeling a drug, placebo-controlled trials would be ethically objectionable given the current strong evidence for naloxone’s safety and effectiveness. More non-controlled studies are possible and may be necessary.

The challenge will be in securing funding from government bodies that are generally reluctant

to support studies exploring potentially controversial interventions.⁴⁹ Because patents on the drug have long expired, market incentives are inadequate for the millions of dollars required to gather sufficient data for a successful relabeling application. Within the competitive pharmaceutical industry, there would be little expectation of a return on investment for any single company from a successful relabeling effort.^{15,48}

CONCLUSION

Naloxone is an eminently safe and nonabusable substance that has 1 pharmacological function: to reverse the effects of opioids on the brain and respiratory system in order to prevent the ultimate adverse event, death. Indeed, one can purchase dozens of more dangerous and abusable substances over the counter at a local drug store. Current medicolegal biases and regulations have nonetheless unduly restricted the availability of naloxone for those who need it most. It is understandable that regulators did not foresee the utility of naloxone as a public health intervention carried out by people who are not medical professionals. In the midst of our current epidemic of accidental deaths related to illicit and prescription opioids, however, these restrictions are untenable. The status quo must be challenged by a public health ethic that seeks to “advocate and work for the empowerment of disenfranchised community members, aiming to ensure that the basic resources and conditions necessary for health are accessible to all.”^{50(p4)}

Three policies capable of increasing access to naloxone should be considered. First, physician prescriptions of naloxone to at-risk patients should be increased, and second, distribution programs should be expanded; both could be accomplished within current regulatory structures. Third, naloxone could be relabeled as an over-the-counter drug, which may be an important alternative that could supplement the limited reach of the first two options, although further studies may be necessary. Each of these policies should be accompanied by appropriate illicit opioid supply and demand reduction measures. There has been a recent surge of interest among parents and community groups looking for options in response to increased opioid misuse in their communities. The Drug Overdose Reduction Act that was introduced in the Senate in 2006 calling for action on surveillance, research, and intervention programs for preventing overdose and associated deaths was at least one promising response. The Bill failed to pass in 2006, but we strongly urge its rapid reintroduction. Continued discussion and action to address the barriers that limit people’s access to this life-saving emergency treatment is urgently needed. ■

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