

## **Testimony Submitted on Behalf of Sandra D. Comer, Ph.D. The College on Problems of Drug Dependence**

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to submit testimony to the Subcommittee. My name is Dr. Sandra Comer and I am the President of the College on Problems of Drug Dependence (CPDD), a membership organization with over 1000 members that has been in existence since 1929. It is the longest standing organization in the United States addressing problems of drug dependence and abuse. The organization serves as an interface among governmental, industrial and academic communities maintaining liaisons with regulatory and research agencies as well as educational, treatment, and prevention facilities in the drug abuse field.

I am also a Professor of Neurobiology in the Department of Psychiatry at the College of Physicians and Surgeons of Columbia University, and a Research Scientist at the New York State Psychiatric Institute. My research focus for over 2 decades has been on the development and testing of novel approaches to the treatment of opioid dependence.

### **Scope of the Problem**

Drug overdose is a major cause of injury and death worldwide. For example, in a recent meta-analysis of mortality among regular users of opioids, Degenhardt and colleagues (2011) evaluated 58 prospective studies from numerous countries around the world and determined that the most common cause of death was drug overdose. In the United States, the single leading cause of injury-related mortality in 2008 was poisoning, nearly 90% of which was attributed to both legal and illegal drugs (Warner et al., 2011). For the first time in almost three decades, the number of fatalities attributed to poisoning (41,000) exceeded the number of fatalities attributed to motor vehicle traffic accidents (38,000). In New York City, the age-adjusted rate of emergency department visits related to heroin was 152/100,000 New Yorkers, which was similar to the rate reported in 2004. By comparison, the rate of emergency department visits related to prescription opioids was 110/100,000 New Yorkers in 2009, which was double the rate reported in 2004 (Epi Data Brief, New York City Department of Health and Mental Hygiene, 2011). The risk factors for opioid overdose are a previous history of overdose (Darke et al., 2007, Wines et al., 2007), recent discharge from detoxification programs (Strang et al., 2003; Wines et al., 2007), initiation or discontinuation of opioid maintenance therapy (Degenhardt et al., 2009), recreational use of prescription opioids (Centers for Disease Control and Prevention, CDC Vital Signs, November 2011; Warner et al., 2011), and recent release from prison (Seaman et al 1998; Wakeman et al., 2009).

In response to this serious public health concern, the United Nations' central drug policy-making body, the Commission on Narcotic Drugs, unanimously approved a resolution in March 2012 to promote measures to prevent drug overdose. In support of this resolution, White House Office of National Drug Control Policy (ONDCP) Director Gil Kerlikowske endorsed the need to train public health and safety personnel to recognize drug overdose and administer life-saving techniques and/or medications, including naloxone. Methadone, buprenorphine, the buprenorphine/naloxone combination and naltrexone are also effective treatment medications that would help reduce overdose fatalities. Each of these options will be discussed below, with a particular focus on more widespread distribution of naloxone to persons who are not medically trained. This description will include a summary of what we do and do not know about use of naloxone in this context.

## **One Potential Solution**

Naloxone is a potent, short-acting medication that acts as an antagonist at opioid receptors. It produces no agonist effects of its own, so the risk of abusing the medication is non-existent. Naloxone is effective in both preventing and reversing opioid agonist effects, including respiratory depression, which is the primary cause of death due to opioid overdose (White and Irvine, 1999). The antagonist effects of naloxone are evident within 5 min following administration, and the duration of antagonism at commonly prescribed doses (0.4-0.8 mg) is 45 to 90 min. It is relatively ineffective orally, so it is typically administered intravenously or intramuscularly and more recently, intranasally (Kelly et al., 2005; Kerr et al., 2009; Merlin et al., 2010). Originally approved by the Food and Drug Administration in 1971 for treating opioid overdose, naloxone is traditionally used in both emergency room and non-hospital settings, where it is administered by medically trained personnel.

Although medical professionals have used naloxone successfully for over four decades, non-fatal and fatal opioid overdoses continue to increase steadily and are now at alarming levels. In an effort to understand the circumstances surrounding opioid overdoses, several survey studies have been conducted among drug users (Baca and Grant, 2007; Lagu et al., 2006; Seal et al., 2003; Strang et al., 2000; Tracy et al., 2005). These studies reveal that a large number of users (64-97%) report that they had witnessed at least one overdose (Lagu et al., 2006; Seal et al., 2003; Strang et al., 2000; Tracy et al., 2005). The majority of witnessed overdoses occurred in the presence of a friend (70%), acquaintance (14%), or partner (10%; Strang et al., 2000). Thus, because many overdoses occur in the presence of a witness and because deaths associated with opioid overdoses typically do not occur instantaneously, programs to educate drug users and other non-medically trained persons, such as first-responders (police officers, firemen, etc.) and family members on how to identify and respond to opioid overdoses have been implemented in various countries around the world, including the United States. A particular interest is in training drug users because they are the ones most likely to witness an overdose event and therefore are able to respond immediately. While educating drug users about risk factors associated with opioid overdose is not controversial, training them on how to intervene has been a subject of much debate. In particular, teaching drug abusers how to use naloxone to reverse an opioid overdose has met with substantial resistance in some circles (Bazazi et al., 2010; Coffin et al., 2003; Tobin et al., 2005).

## **Potential Barriers**

### *Legal Barriers*

One immediate concern with prescribing naloxone to drug users, first responders, and family members is its legal ramifications (Burriss et al., 2009). Naloxone is not considered a controlled substance by the Drug Enforcement Agency, meaning that it is not considered to have abuse potential, but it is classified by the Food and Drug Administration as a prescription medication. Therefore, properly licensed individuals (physicians, nurse practitioners, physicians' assistants, etc.) must prescribe the medication to patients. However, in a few programs in the U.S. and abroad, naloxone is being prescribed to a person who would most likely use it to reverse another person's drug overdose, which raises questions about legal liability for both the prescriber and the person who used the medication on another person. In most states in the U.S.,

dispensing naloxone in this way is illegal (Burris et al., 2009). In response to this legal quagmire, several states have now passed legislation authorizing naloxone programs and participation by non-professional individuals. New Mexico, in 2001, was the first state to allow naloxone distribution to “lay savers” and “immunity to doctors who administer naloxone to others” (Burris et al., 2009). In 2005, New York passed laws that were similar to those passed in New Mexico. In other states, specific counties (in California) or cities (Boston, Baltimore) received legal authority to dispense naloxone to drug users and drug non-users for the purpose of reversing opioid overdose in another person. As of December 2014, about half of the states in the U.S. have passed laws allowing for the “prescribing and administration of naloxone and/or criminal protections for bystanders who seek emergency assistance” (Hardesty, 2014 - <https://www.whitehouse.gov/blog/2014/12/17/updated-infographic-overdose-prevention-state-state>).

Although this is a good start, much work remains to be done. Efforts are being made to expand access to naloxone in other states and possible re-labeling of naloxone by the FDA as an over-the-counter medication is being pursued (Kim et al., 2009; Burris et al., 2009). On April 12, 2012, the FDA convened a “scientific workshop to initiate a public discussion about the potential value of making naloxone more widely available outside of conventional medical settings to reduce the incidence of opioid overdose fatalities” (Federal Register Notice, 2011). In the meantime, empirical data on the effectiveness of naloxone programs in reducing fatal overdoses, as well as the complications associated with non-fatal overdoses, is critically needed.

#### *Resistance by Medical Personnel*

In addition to worries about the legal implications of dispensing naloxone to drug users, other concerns have been raised by medical personnel regarding this practice. For example, Tobin and colleagues (2005) conducted a survey among 327 emergency medical service providers and found that most (56%) of the providers felt that training drug users and other non-medically trained persons to administer naloxone would not be effective in reducing overdose deaths. The most common concerns were that non-medical persons would not be trained to administer naloxone properly, and that they would not know how to accurately identify opioid overdoses. In addition, concerns were raised that drug users specifically would feel that the medical providers were condoning their drug use. In another survey of 363 health care providers (physicians, nurse practitioners, physicians’ assistants), 37% reported that they would not consider prescribing naloxone to patients at risk of heroin overdose, 33% reported that they would consider it, and 29% were unsure (Coffin et al., 2003). The reasons that they objected to prescribing naloxone to drug users were not queried, but it is likely that concerns about safety are part of the reasons for the reluctance to prescribe naloxone to drug abusers. One potential problem is that because the half-life of naloxone is shorter than heroin, a recurrence of severe respiratory depression could emerge if emergency personnel were not called and the victim was left unattended after the initial dose of naloxone was administered. Several studies, however, have demonstrated that under most circumstances, a single administration of naloxone is sufficient to provide a sustained reversal of life-threatening respiratory depression (Etherington et al., 2000; Rudolph et al., 2011; Vilke et al., 2003; Wampler et al., 2011).

In another study, cardiac complications and pulmonary edema, as well as violent behavior were reported within 10 minutes after naloxone was administered to patients (Osterwalder, 1996). However, others have reported that cardiac rate and rhythm

improve after naloxone is administered to patients in cardiac arrest (Saybolt et al., 2010). And yet others have concluded that although adverse events associated with naloxone administration during suspected opioid overdose are common (e.g., confusion (32%), headache (22%), nausea/vomiting (9%), aggressiveness (8%)), serious complications (e.g., seizures (4%)) are rare (Buajordet et al., 2004). The study by Buajordet and colleagues (2004) was conducted in out-of-hospital settings where paramedics administered naloxone. Prospective and detailed information about the potential adverse events surrounding naloxone use by drug abusers is needed, given that the incidence of adverse events surrounding naloxone use by medically untrained persons is likely to be higher than when it is used by medical personnel.

#### *Resistance by Drug Users*

While medically trained personnel have multiple concerns about dispensing naloxone to drug users, the drug users themselves have expressed concerns about intervening during overdose episodes among peers. One of the most common reasons cited by drug users for failing to call, or delaying a call, for medical assistance during an overdose was the fear of police involvement, while others reported that they believed that they could handle the event themselves (Tracy et al., 2005; Worthington et al., 2006).

Unfortunately, in untrained drug users, common methods used to reverse overdose, such as immersing the victim in cold water, injecting cocaine, milk, or salt water, or pouring milk into the victim's mouth, are relatively ineffective or potentially harmful (Seal et al., 2003). Among those who had received naloxone in the past, 82% reported that the experience was extremely unpleasant (Seal et al., 2003), suggesting that previous exposure to naloxone may be a deterrent to its use among some drug abusers.

Nevertheless, the majority (79%) said that they would want to receive naloxone if they overdosed and an even larger majority (87%) reported that they would be willing to participate in a program that provided naloxone and training on how to use it (Seal et al., 2003). Other studies have reported similar outcomes in terms of drug users' willingness to use naloxone to reverse overdose in a peer (Lagu et al., 2006; Strang et al., 1999). Thus, despite concerns about police involvement, most drug users appear to be open to the idea of peer-administered naloxone to treat overdose.

#### *Unintentional Negative Consequences*

Although drug users reported a willingness to administer naloxone if trained in its use and would want others to administer it to them if they overdosed, a subset of users (35%) admitted that they would feel more comfortable using greater amounts of heroin if naloxone was readily available (Seal et al., 2003). Furthermore, 62% of respondents said that they would be less likely to call 911 if naloxone was available during an overdose episode. Other objections to naloxone programs that have been cited are that drug users would be more likely to initiate heroin use if naloxone was readily available (Sporer, 2003) and that they would be less likely to seek treatment for their drug use if the perceived negative consequences of using drugs were reduced (Bazazi et al., 2010). To date, however, these latter two concerns have not been studied sufficiently.

### **Current Data on Naloxone Distribution Programs**

In February 2012, the Centers for Disease Control and Prevention published the results of a brief online survey of 50 naloxone distribution programs in the U.S. (Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, February 17, 2012). A total of 48 programs responded to the survey from 15 states and the District of Columbia. An estimated total of 53,032 individuals have received naloxone as a take-

home medication and 10,171 overdose reversals have been reported. Many of these programs have successfully implemented naloxone as a routine part of opioid overdose prevention efforts. For example, between 2005 and 2008, 426 individuals in Pittsburgh and Allegheny County, Pennsylvania received naloxone, and 89 reported administering it during 249 individual overdose episodes (Bennett et al., 2011). Of these 249 episodes, 96% were successfully reversed, 3.2% had unknown outcomes, and 0.8% (2 cases) were unsuccessful. Between March and December 2005, 122 individuals in New York City received naloxone, and 50 reported administering it during 82 individual overdose episodes (Piper et al., 2008). Of these 82 episodes, 83% were successfully reversed by naloxone and 17% of the outcomes were unknown. Other programs have reported similar rates of naloxone use and positive outcomes in the U.S. (Doe-Simkins et al., 2009; Enteen et al., 2010; Galea et al., 2006; Maxwell et al., 2006; Seal et al., 2005; Tobin et al., 2009; Wagner et al., 2010; Yokell et al., 2011) and abroad (e.g., Dettmer et al., 2001; Hurley, 2011; Strang et al., 2008).

These findings are encouraging and many studies suggest that the impact of naloxone on overdose death rates is positive. For example, after naloxone prescribing was instituted in 2001 in Chicago, 10-20% decreases in heroin overdose deaths were reported between 2001 and 2003 (Maxwell et al., 2006). This trend was noteworthy because a four-fold increase in heroin overdose deaths had occurred in Chicago between 1996 and 2000. Reductions in death rates have also been reported in Massachusetts (Walley et al., 2013). And in Wilkes County, North Carolina, where community efforts to reduce opioid overdoses were instituted, the overdose death rate dropped sharply from 46.6 per 100,000 in 2009 to 29.0 per 100,000 in 2010, whereas overdose deaths increased during the same time period in virtually every other county in North Carolina (Albert et al., 2011). However, naloxone prescribing to drug and non-drug users were implemented relatively late in the program in Wilkes County, so the impact of naloxone per se on overdose death rates is not entirely unclear.

In Western Australia, Hargreaves and colleagues (2002) conducted a time-series analysis that covered the period of time before and after implementation of overdose prevention programs that included dissemination of overdose prevention information to drug users and increased use of naloxone by ambulance staff. These investigators found that after an initial reduction in heroin-related fatalities, their effectiveness declined over time. Because naloxone was not prescribed to drug users in Western Australia (it was only used by emergency medical personnel), it is likely that the reduction in fatalities was due to education alone, which is encouraging. However, the decline in effectiveness over time is a concern. Although the studies in Chicago and Massachusetts suggest that distribution of naloxone may have a measurable effect on overall opioid overdose death rates, no other studies have confirmed this finding. Clearly, more information is needed on this important topic (Compton et al., 2013).

In addition to the need for more empirical evidence of the effectiveness of overdose training and naloxone distribution programs in reducing rates of opioid overdose, some studies suggest that greater efforts could be directed toward improving the training programs themselves. For example, 46 opioid-dependent patients in London and Birmingham who were trained in recognizing and managing opioid overdose showed only partial retention of information 6 months later (Gaston et al., 2009). The number of correct responses increased significantly immediately after training, but steadily declined over time (Gaston et al., 2009). Furthermore, while 80% of the sample (37/46) still had the naloxone that had been prescribed to them 6 months previously, most of them (81%)

kept it at home, where it would only be useful if the overdose happened to occur in their home environment (Gaston et al., 2009). Reasons cited for not carrying the naloxone with them were fear of police involvement, concerns about stigma associated with carrying injection material (a “mini-jet” naloxone formulation was used that included a needle), and the inconvenience of carrying bulky items. Overall, the authors concluded that “training individuals does not seem to be sufficient for these programmes to succeed and a more systematic approach is necessary” (Gaston et al., 2009).

The recent availability of intranasal formulations of naloxone may partly mitigate drug users’ concerns about carrying naloxone with them, but more concerted efforts are needed to emphasize the importance of keeping naloxone with them at all times. In addition, longer-term assessments of retention of knowledge should be conducted to determine whether “refresher” trainings are needed and when they should be provided. And finally, other approaches to improving the effectiveness of the training programs should be considered, such as training a drug-using partner or significant other in recognizing and managing opioid overdose.

### **Other Options for Reducing Overdose Death Rates and Need for Further Research**

Several effective medications are currently available for treating opioid dependence, including methadone, buprenorphine, buprenorphine in combination with naloxone, and naltrexone, and they all have advantages and disadvantages. For example, methadone has been used for decades to treat opioid dependence and its clinical utility is clear (Strain and Stitzer, 2006). However, the stigma associated with methadone maintenance and the inconvenience of daily visits to methadone clinics make this an unattractive option for many abusers, particularly those who may have recently started abusing prescription opioids. Buprenorphine, a partial mu opioid agonist and kappa opioid antagonist, also effectively reduces opioid abuse and dependence (e.g., Carrieri et al., 2006). It is a safer medication than methadone in that it is much less likely to cause clinically significant respiratory depression (Walsh et al., 1994). The ability to obtain buprenorphine from physicians’ offices also makes it an attractive treatment option. However, induction onto buprenorphine is sometimes difficult because it can precipitate withdrawal symptoms in individuals who are heavily dependent on opioids, especially longer-acting ones such as methadone (Levin et al., 1997; Walsh et al., 1995). Buprenorphine itself also has abuse potential and, in some countries, has largely replaced heroin as the opioid of choice among intravenous drug abusers (Alho et al., 2007; Comer et al., 2005; Lee, 2006; Obadia et al., 2001). While the buprenorphine/naloxone combination appears to have lower abuse potential than buprenorphine alone, it also has some abuse liability (e.g., Comer and Collins, 2002). Naltrexone, an opioid antagonist, is effective in virtually eliminating the agonist effects of heroin and other opioids (Comer et al., 2002; Navaratnam et al., 1994; Schuh et al., 1999; Verebey et al., 1976). However, compliance with medication ingestion is a problem clinically, leading to low treatment success. Sustained-release formulations of naltrexone are potential solutions to this problem and several studies are currently underway to determine whether this treatment option will be effective in the long-term management of opioid dependence (e.g., Comer et al., 2007). While the available agonist and antagonist medications are effective in reducing opioid abuse and dependence, the associated difficulties with their use highlight the need for novel medication approaches for the treatment of opioid dependence.

## **Summary**

In summary, several treatment medications are currently approved by the FDA including methadone, buprenorphine, buprenorphine/naloxone, and naltrexone for treating opioid use disorders as maintenance medications, and naloxone for treating opioid overdose. All of these medications have proven to be effective, but much remains to be done both legislatively and clinically to improve their impact. Legislatively, increasing the availability of methadone, buprenorphine, buprenorphine/naloxone, naltrexone and naloxone to those with OUD will help combat this problem. Clinically, conducting research to determine the most effective ways of using the medications and targeting the interventions to suit the needs of individual patients is still needed.