REPORT:

Health Security Workshop on Mass Casualties from the Deliberate Release of Opioids

Hosted by Global Health Security Initiative Chemical Events Working Group

November 6-7, 2018, Boston, MA

ABSTRACT

Opioid use disorder (see Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, American Psychiatric Association, for diagnostic criteria) has evolved into a public health crisis in some parts of the world since about the late 1990s. To meet the demand, massive amounts of illicit opioid drugs have flooded those geographic areas as well as the locations where they are manufactured and through which they are transported. With this greatly increased availability of highly potent opioid substances, the risks of their deliberate use as weapons or the unintentional poisoning of large numbers of people, potentially causing a mass casualty incident, have risen. The Global Health Security Initiative (GHSI) Chemical Events Working Group conducted a workshop on November 6-7, 2018 to explore the risks, the current state of medical and public health preparedness for a mass casualty opioid incident, and opportunities to enhance that preparedness.

INTRODUCTION

Certain pharmacological properties of opium, the exudate of the unripe seed capsule of the poppy plant *Papaver somniferum*, were recognized several millennia ago. Since that time, people have ingested and smoked opium for relief from pain and other ailments, for sedation, and recreationally for its euphoric effects. During the eighteenth and nineteenth centuries, international trade in opium grew, with Western countries exporting large amounts to China, opium dependence becoming a problem for Chinese society, and two Opium Wars erupting in the mid-1800s. Recreational opium use and dependence also spread to other countries in Asia and Europe and to the United States.

The medicinal benefits of opioids gained widespread acceptance and use by the professional medical community with the isolation of morphine, in 1804, and codeine, in 1832, from opium. Morphine is very effective at relieving severe pain; codeine is prescribed to relieve moderate pain and for cough suppression. Later in the 1800s, scientists began attempting to produce a non-addictive opioid. Heroin, synthesized from morphine, was introduced into medical practice in 1898. Although its addiction potential was apparently initially unrecognized, all heroin use was made illegal in the United States in 1924 after addiction and abuse afflicted many and became a public health issue. Other semi-synthetic opioids such as oxycodone and hydrocodone, made from the natural opium-derived substances thebaine and codeine, were introduced in the early 1900s. These drugs became widely prescribed analgesics. Fentanyl, completely synthetic, was produced in 1960 and has come to play a crucial role in medicine as a safe, short-acting analgesic and anesthetic. Two compounds closely related to fentanyl, sufentanil and alfentanil, serve similar clinical purposes.

All of the drugs described above have addiction potential. Further, they can cause dangerous adverse effects at doses higher than those recommended for therapeutic benefits. The most serious is respiratory depression, which can be fatal, and is the cause of many opioid overdose deaths. Synthetic opioids have a history of use as weapons. In the best known case, Russian authorities in 2002 disseminated a toxic substance, which evidence suggests was a mixture of remifentanil and carfentanil, through the ventilation system of a Moscow theatre during a standoff with Chechen rebels who had taken approximately 900 people hostage. Reportedly the Russians' intent was to incapacitate the hostage-takers by utilizing the fentanyl-like compound's anesthetic properties, providing an opportunity to rescue the hostages. However, more than 120 hostages died and hundreds more were hospitalized after receiving an uncontrolled dose of the substance introduced by the weapon system. Healthcare response efforts were hampered because clinicians did not know what agents the Russian authorities had employed. Due to their high potential lethality and ease of dissemination, fentanyl and its analogues have also been implicated in attempted and successful assassinations.

The current opioid public health crisis began in the late 1990s when pharmaceutical companies started aggressively marketing prescription opioids to relieve chronic pain while falsely claiming they posed low risk of addiction. Since then, opioid dependence, use disorder, overdoses, and deaths from overdose have skyrocketed in the United States and Canada. The illicit market is thriving, placing large quantities of various opioids "on the street." The accessibility of these substances (many are also relatively inexpensive) as well as their high potency, ease of dissemination, and historical use as weapons

prompted the GHSI Chemical Events Working Group to conduct a multi-disciplinary, multi-jurisdictional workshop to discuss the risks of an opioid mass casualty incident.

GHSI (http://ghsi.ca/) is an informal international partnership among like-minded countries to strengthen health preparedness and response globally to threats of biological, chemical, and radio-nuclear terrorism, and pandemic influenza. This initiative was launched shortly after the September 11, 2001 attacks in the United States. Canada, the European Union, France, Germany, Italy, Japan, Mexico, the United Kingdom, and the United States are members. The World Health Organization serves as an expert advisor. One of the major aims of the partnership is to address emerging threats to health security.

GOAL OF WORKSHOP

The goal of this workshop was to provide participants with an opportunity to identify the key clinical and public health challenges, opportunities, limitations, and actions necessary when responding to a mass casualty incident involving the deliberate release of an opioid.

WORKSHOP OBJECTIVES

- Assess the feasibility and impacts of a large scale opioid attack on the public
- Explore measures to prevent or mitigate mass exposure to opioids
- Identify challenges to clinical and public health preparedness and response for an intentional opioid release
- Identify lessons learned from the Novichok incident in Salisbury, U.K. and evidence from responses to fentanyl incidents
- Discuss the optimal products, distribution, and locations to stockpile medical countermeasures for response to a mass casualty opioid incident
- Discuss the research and development needs for opioid antidotes
- Capture key points regarding the current state of play; record key gaps and how they may be addressed

WORKSHOP PARTICIPANTS

Emergency responders and hospital-based receivers, public health professionals, clinicians, poison center specialists, toxicologists, researchers, emergency planners, law enforcement officers, policy makers, and others active in protecting the health of the public attended the workshop. These participants represented local, state, and federal governments within the United States as well as Canada, the European Commission, Germany, Japan, Mexico, and the United Kingdom.

WORKSHOP SCENARIO

A credible scenario in which unknown assailants deliberately release an opioid within an indoor environment, causing mass casualties, was presented at the beginning of the workshop to establish a common operating picture and reference for discussion.

KEY POINTS EXPRESSED BY PRESENTERS AND PARTICIPANTS (BY OBJECTIVE)

OBJECTIVE ONE: ASSESS THE FEASIBILITY AND IMPACTS OF A LARGE SCALE OPIOID ATTACK ON THE PUBLIC

Facilitated by Danny Sokolowski, Health Canada, Chemical Emergency Management and Toxicovigilance Division

Assessment of the Feasibility: Jessica Cox, U.S. Department of Homeland Security, Science & Technology Directorate, Chemical Security Analysis Center

The U.S. Department of Homeland Security established the Chemical Security Analysis Center (CSAC) in 2006 to understand and mitigate toxic chemical threats and hazardous chemical processes. CSAC uses an integrated capability platform based on modeling, simulation, and core subject matter expertise to perform chemical hazard analysis, chemical threat characterization, and chemical emergency surveillance and response. Jessica Cox described CSAC's assessment of opioids as potential weapons to cause mass casualties.

First, Ms. Cox summarized the general terrorism landscape. Approximately 170,000 terrorist attacks occurred worldwide between 1970 and 2015, with more than 3,000 incidents taking place in North America. Most attacks occurred in the Middle East and South Asia. The terrorism weapons of choice remain explosives (89,693 incidents) and firearms (60,802 incidents). Chemicals rank 5th, as they were used as weapons in 348 incidents worldwide including 29 in North America.

The number of chemical terrorism events globally has steadily increased since 2011. Routine use and dependency upon a large number of highly toxic compounds for industrial and household purposes make them a weapon of opportunity. Chemical agents that have actually been employed as weapons include corrosives, metals, cyanide, pesticides, and chemical warfare agents such as sulfur mustard, nerve agents, and chlorine.

With pharmaceutical compounds such as opioids, the global market paves the way to global threat. In particular, fentanyl and its analogues exist in a variety of structures sharing properties such as high potency (fentanyl is 80-100 times more potent than morphine), stability, solubility in alcohols and moderate solubility in water, as well as rapid symptom onset. Opioids are low cost, relatively easy to manufacture, and even easier to procure illicitly, for example via the dark web. Outside

of a healthcare setting, they have been used in the past with the intent to incapacitate; but in the Moscow theatre siege, opioids did more than just incapacitate, killing at least 120 people. Opioids can be employed in a variety of scenarios, including closed buildings, arenas, outdoor environments, food, and distributed items. Scenarios of contaminated food and distributed items have dispersion in space and time, which can pose a challenge to finding the source.

The CSAC assessment concludes that a deliberate release of opioids is feasible. The combination of high potency, wide availability, and ease of dissemination make opioids a credible weapon of opportunity.

What are the Risks to Health Security? Mark Kirk, U.S. Department of Homeland Security, Office of Countering Weapons of Mass Destruction, Chemical Defense Program

In addressing opioids, Dr. Kirk emphasized that it is essential to be prepared to recognize a deliberate release, since a delay in recognition and treatment will increase the numbers of fatalities and morbidities. Exposure to opioids offers a small window of opportunity for successful treatment. But this is also true for the acute health effects of many other chemicals. Therefore, efforts to improve preparedness and response for a deliberate opioid incident are relatively easy to integrate into general chemical preparedness and response planning.

The U.S. Department of Homeland Security's Chemical Defense Program has analyzed local communities' response systems for potential impacts, challenges, and current capabilities with regard to chemical incidents in general. The goal was to identify leverage points where additional effort and resources can have the greatest impact to improve the systems' capabilities.

The analysis highlighted four major leverage points:

- Prime the pump – understanding a community's unique chemical risks can help the response system be prepared for the most likely types of incidents
- Early recognition – early recognition increases the potential for rapid actions to be effective in improving medical outcomes
- Stop the exposure – evacuation from the site of chemical release and patient decontamination can prevent or minimize the amount of chemical absorbed into the body and thereby the dose received, which in turn reduces the adverse health effects
- Treat the wounded – emphasize supportive care first (e.g., airway, breathing, circulation) and medical countermeasures, such as naloxone for opioid poisoning, second; anticipate scarce resource situations by forecasting needs and developing advance plans for alternative sources and alternative treatments

Dr. Kirk described an outbreak of severe opioid toxicity in Sacramento, CA in 2016. Over an 8-day period, 18 patients presented to a single hospital. Seventeen of the patients required naloxone and many required significant additional medical interventions. Higher doses and more prolonged infusions of naloxone were required than expected. This outbreak overwhelmed local and regional resources. Antidote stocking was inadequate and emergency deliveries were required. Even a relatively small scale incident such as this can trigger a scarce resource situation.

Dr. Kirk concluded that since a small window of opportunity exists to respond to rapid-acting chemical exposures such as opioids, time is key: swift actions save lives. Optimizing the leverage points described above can improve medical outcomes. A successful response requires prior emergency planning and preparedness as part of a multi-disciplinary, multi-agency approach.

The Health Security Threat Opioids Represent in Europe: Michael Evans-Brown, European Monitoring Centre for Drugs and Drug Addiction

The rapidly evolving chemical landscape of synthetic opioids is of growing concern worldwide, including in Europe. Michael Evans-Brown presented findings of the European Monitoring Centre for Drugs and Drug Addiction. The Centre runs the European Union (EU) Early Warning System, which analyzes information from 30 national early warning systems, including epidemiology, law enforcement seizures, laboratory analyses, and open source reports. Since 2012 there have been increasingly greater amounts of illicit opioids on the European market. Although distribution is not uniform, it is prevalent in all countries. The EU Early Warning System issues a formal notification to member countries of new compounds identified; laboratories can then add these structures into their monitoring programs.

The number of new fentanyl analogues identified in Europe increased between 2012 and 2018, most sharply since 2016. China is a major producer of fentanyl analogues but domestic production is expected to increase as international regulations increase. Fentanyl synthesis is not difficult and crude laboratories have been found in many places, including private homes.

Mr. Evans-Brown stressed that threat awareness is important because fentanyl and its analogues, such as carfentanil, are readily accessible, possess high potency, and can produce significant health consequences. As opioids are fast acting compounds, typical chemical/biological/radiological/nuclear (CBRN) response protocols may need to be modified. The EU Early Warning System reduces the risk of acute harm by enabling information exchange, threat detection, assessment, prioritization, response, and risk communication. Early warning systems are critical to protecting health by enhancing awareness, preparedness, and response.

OBJECTIVE TWO: EXPLORE MEASURES TO PREVENT OR MITIGATE MASS EXPOSURE TO OPIOIDS

Facilitated by Agnes Molnar, European Commission, Directorate-General for Health and Food Safety

Tackling the Opioid/Fentanyl Threat: James DiSarno, U.S. Drug Enforcement Administration

Mr. DiSarno summarized key points about the availability of opioids based on the U.S. Drug Enforcement Administration's (DEA) enforcement actions and analyses. Many chemical modifications to the fentanyl molecule are possible and this is reflected in what is available through illicit means. The DEA has identified a large number of new synthetic opioid compounds among their seizures in the last several years: 450 new compounds during the years 2009-2014 and 50 new compounds in 2015-2017. The number of fentanyl analogues identified varies geographically but is increasing throughout the United States. Most illicit opioids are manufactured in China and Mexico and reach the U.S. through major ports of entry in California and Florida. Fentanyl imported in this way is usually of low purity (average ~2-6%), though some is more pure. Assessing the availability of various illicit drugs over the first nine months of 2018 for the U.S. as a whole, methamphetamine was most prevalent (34%), followed by cocaine (20%), heroin (15%), marijuana (5%), fentanyl (5%), and others; in the Northeast U.S., heroin (28%) was most prevalent, then cocaine (25%), fentanyl (12%), oxycodone (6%), methamphetamine (5%), and others.

As of March 1, 2017, China banned the legal manufacture and sale of carfentanil, furanyl fentanyl, acrylfentanyl, and valeryl fentanyl. Mr. DiSarno suggested that India may become another major source of illicit opioids, especially if China continues to regulate these chemicals; in September 2018 the Indian government recovered 9 kg of fentanyl from an illegal lab. Laos and Cambodia could also become locations for large scale illicit manufacturing of opioids for the global market. Clandestine labs are not difficult to create. Rudimentary equipment will work: synthesis requires steps to mix and stir, filter, and isolate, but no heating, refluxing, or distillation are required. Labs have been discovered in crowded garages and warehouses. Some illicit manufacturers have the ability to produce pills that are very difficult to distinguish by sight from legitimate products.

Law enforcement officers should be aware of the potential risks of exposure to fentanyl and other opioids. Mr. DiSarno recommended that officers likely to come into direct contact with opioids protect their airways and exposed skin using the appropriate protective devices. The most suitable types of protective equipment will differ depending on the circumstances. Use caution when handling fentanyl, fentanyl analogues, or items suspected to include any such substances. U.S. Government guidance recommends that people clean exposed skin with water, and soap if available, but avoid using alcohol-based sanitizer based on the possibility that it may increase absorption of the drug through the skin.

Regulatory Measures for Rational Use of Controlled Medicines: Jose Herrera, Federal Commission for Protection Against Sanitary Risks, Health Ministry, Mexico

Jose Herrera described the Mexican government's work to achieve a balance between allowing legitimate beneficial use and preventing abuse of and illicit activities associated with opioids. The Mexican government regulates the supply chain of narcotics and psychotropic substances for the purposes of (1) allowing and promoting use for therapeutic and scientific purposes, (2) minimizing the risk of abuse, and (3) reducing the risk of their illicit production, demand, and traffic. In 2013, according to the World Health Organization, Mexico's per capita consumption of morphine was 54% lower than the worldwide average. Mexico created an inter-institutional group that included representation from the National Health Council, the pharmaceutical industry, medicine distributors, retail pharmacists, national hospitals, non-governmental organizations, the Supreme Court, and the Federal Commission for Protection Against Sanitary Risks (COFEPRIS). The group's objectives were to develop a national strategy for pain control and palliative care, assure an adequate supply of morphine, and develop regulations to integrate palliative care into all national health system institutions. As a result, it became mandatory for all health institutions to have operational and overall policy schemes for palliative care. In addition, COFEPRIS created electronic prescription books for opioids, which provide for strict and detailed control of prescriptions issued in each pharmacy. Through prescription books, prescriptions are validated in pharmacies and all medicines are traceable.

The inter-institutional group continues to promote its tools as well as monitor inventories of morphine throughout Mexico. It has written a guide for selling controlled medicines in pharmacies that concentrates all regulatory information in one place. The group is also analyzing the effects of its current measures in order to fine tune them and generate new public policies. Mr. Herrera showed that for Mexico, information technology is fundamental to improved regulatory capacity, which in turn has facilitated access to controlled medicines while promoting their rational use.

OBJECTIVE THREE: IDENTIFY CHALLENGES TO CLINICAL AND PUBLIC HEALTH PREPAREDNESS AND RESPONSE FOR AN INTENTIONAL OPIOID RELEASE

Facilitated by Luke Yip and Renee Funk, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

The facilitators, Luke Yip and Renee Funk, asked representatives of stakeholder organizations (e.g., first responders, hospitals, poison control centers, clinical toxicology laboratories, and public health) to engage in an interactive exchange about their respective roles and responses in the workshop scenario. This discussion helped

to inform on current preparedness as well as challenges for clinical and public health response to a mass casualty incident from deliberate opioid release. Each of the following paragraphs summarizes a challenge or element of preparedness and/or response to a mass casualty opioid incident along with applicable conclusions from the group's discussion.

During the initial stage of a chemical incident, medical personnel may have to operate with limited understanding about the nature of the incident or knowledge of the chemical's characteristics. Intelligence and information sharing are critical to first responders' approach to the scene of an incident. In contrast to a biological outbreak, victims of a deliberate opioid release may rapidly succumb to life-threatening respiratory depression that requires rapid medical response and use of medical countermeasures before laboratory confirmation or identification of a specific chemical agent. Additionally, laboratory testing for specific opioid(s) may not be acutely important or needed because opioid toxicity is a clinical diagnosis and treatment is empiric. Ideally, patient decontamination will not delay medical treatment. Decontamination should be risk-based; disrobing and otherwise removing any visible powder may be sufficient depending on the circumstances.

The primary medical countermeasure to opioid toxicity is active airway management (e.g., bag valve mask and/or endotracheal intubation) and mechanical ventilation. This requires a commensurate number of skilled healthcare providers and sufficient equipment to perform such procedures for the number of casualties. Naloxone is an antidote that antagonizes the effects of opioids in the central nervous system and is an important acute pharmacologic therapy for opioid toxicity. However, treatment of opioid toxicity with naloxone is not a substitute for the primary medical countermeasure. Naloxone can be administered by various routes (e.g., intravenous (IV), intramuscular (IM), and intranasal (IN)), and their respective pharmacokinetic profiles have important clinical implications that should be considered when administering naloxone to patients in a mass casualty situation. Naloxone's onset of action will be slower with IM and IN compared to IV administration, but IM and IN may be easier and faster to accomplish in a mass casualty incident.

Hospital stocking of naloxone may be limited and actual naloxone inventory varies among hospitals. One recommendation on naloxone stocking is an amount sufficient to treat a 100 kg (220 pounds) patient for either 8 or 24 hours, 20 mg or 40 mg, respectively. A hospital that has stocked a total of 40 mg might exhaust its naloxone supply during a mass casualty incident. The duration of clinical effects of naloxone is around 30 to 45 minutes after the IV route, which is a narrow window of opportunity to replenish a sufficient quantity of naloxone for patients who need repeated dosing. Medical response surge capacity can be quickly overwhelmed during a mass casualty incident, which creates a scarce resource environment. In this environment, patient triage and resource coordination and utilization (e.g., airway equipment, naloxone) are essential. Emergency acquisition of naloxone may be possible through neighboring hospitals, commercial pharmacies, and pharmacy distribution centers.

Crisis and emergency risk communication (credible, clear, concise, and timely communication and messaging) to stakeholders during a mass casualty incident is critical. Poison control centers have the experience and subject matter experts, and are poised to handle a surge in call volume from the public, healthcare providers, health departments, and media. In addition, poison control centers are a valuable resource to provide messaging for government agencies to share with the public.

Training members of the public to recognize opioid poisoning or toxidrome, provide Basic/Advanced Life Support, and possibly administer naloxone to victims can help save lives until Emergency Medical Services personnel arrive. In addition, trained members of the public may contribute to a medical response surge capacity. Another opportunity is to stage more functional exercises that better identify gaps in the response phase of a deliberate opioid release incident. Lastly, while mitigation, preparedness, and response phases are well covered in this workshop, the recovery phase deserves more attention.

OBJECTIVE FOUR: IDENTIFY LESSONS LEARNED FROM THE NOVICHOK INCIDENT IN SALISBURY, U.K. AND EVIDENCE FROM RESPONSES TO FENTANYL INCIDENTS

Facilitated by Kai Kehe, Germany, Bundeswehr CBRN Medical Defense

Opioid or Organophosphorus Agent? Lessons for Diagnosis and Treatment from the Salisbury Incident: Peter Blain, Public Health England

Peter Blain provided an overview of the Salisbury incident, which is believed to have been an intentional poisoning. On March 4, 2018, two casualties were found on a park bench in Salisbury: a young woman slumped against an older man. The woman was unconscious while the man was staring into space and mumbling. The casualties presented with neither classic cholinergic crisis nor predominant opioid poisoning but with signs that overlapped both toxidromes. Signs and symptoms were somewhat different in each patient. They were found in a location frequented by recreational drug users at a time when emergency responders had recently been alerted to be prepared for synthetic opioid poisoning cases. Based on the context and clinical presentations of miosis, respiratory depression, and altered conscious state, emergency responders initially diagnosed opioid poisoning and administered naloxone.

Neither individual responded clinically to naloxone. In addition, local police suggested that hospital staff should run

an internet search on the male patient because he is a former Russian spy. With these additional pieces of information, clinicians started to consider other types of poisoning, contacted the National Poison Information System, and had blood samples tested for cholinesterase levels. Both patients had very low or undetectable acetylcholinesterase and butyrylcholinesterase. The working diagnosis then changed to organophosphorus poisoning. Blood samples were also sent to the nearby Defence Science and Technology Laboratory in Porton Down. The lab eventually identified a Novichok, an organophosphorus compound also known as a fourth generation agent, in the blood samples.

Pre-existing arrangements for civil and military cooperation in scientific and clinical advice on CBRN agents were implemented in the form of a Clinical Expert Group. For example, this group held daily teleconferences with the local hospital staff and were available 24/7 to support the work of patient care, protecting staff, decontamination, and other issues. The patients received a complex treatment regimen and intensive care for 37 days (female patient) and 73 days (male patient). This was very demanding of hospital staff but they responded very well. No indications of poisoning of medical responders or hospital staff were observed.

U.K. government officials, responders, and clinicians outlined important lessons from this and the subsequent accidental Novichok incident.

Key Lessons for the Health Sector:

- Among the first responders, established protocols worked. But training needs to reemphasize differential diagnosis of organophosphorus vs. opioid poisoning using the triad of signs: miosis, respiratory depression, and altered conscious state.
- Good supportive treatment is critical. Emergency department and intensive care unit staff also need training in CBRN syndrome recognition.
- The Clinical Expert Group – a mix of civilian and military experts – was critical as a source of specialized expertise and experience to support responders and caregivers.
- Police need to understand clinical priorities in treatment of patients.
- The government needs to maintain a cadre of experts with security clearance and capability for secure remote communications.

Key Lessons on Messages to Public and Health Staff:

- Risk assessments need to be dynamic in response to new information.
- Information may be limited for security reasons but more will become available over time.
- Authorities may be criticized for being "too slow" while waiting for certainty and/or "scare mongering" or "lack of grip" when messages change.
- Public and staff can be confused by changes in message; strive for consistency when possible.
- Community engagement is critical to success.

Myths and Misinformation about Casual Dermal Exposure to Fentanyl among First Responders and Law Enforcement: Lewis Nelson, Rutgers New Jersey Medical School

Lewis Nelson discussed the risks of fentanyl exposure to emergency responders and the problematic communication of information that overestimates those risks. The fentanyls (including analogues), although highly potent, are no more dangerous than other opioids. A drug's health effects are dependent on dose, as determined by the specific drug's dose-response relationship, and not simply on potency. All other things being equivalent, drugs of lower potency simply have to be administered at higher doses to have the same clinical effect as high potency drugs.

Fentanyl absorption through intact skin is relatively slow, and rapid onset symptoms after dermal exposure is highly unlikely. Fentanyl used for medical purposes via transdermal administration is specifically formulated to enhance skin permeation and placed in an adherent patch, yet reaching clinically relevant concentrations in the body still takes hours. Thus, casual dermal exposure to powdered fentanyl should be of limited concern to law enforcement officers and other first responders. Many cases of presumed accidental poisoning during the course of a police or medical response have been reported in the media. However, few have been thoroughly investigated and there is no evidence of responders or clinicians developing clinical effects after responding to a scene or treating patients with an opioid overdose.

Two Health Hazard Evaluations by the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health, published in August and September of 2018, were highlighted. In one case, a law enforcement officer was accidentally exposed to a substance, later confirmed to contain fentanyl and methamphetamine, after opening a container of powder which was then blown on them and their uniform by a gust of wind. The officer was wearing a short-sleeved shirt and no gloves. This individual felt lightheaded, disoriented, and experienced blurry vision but did not experience specific signs of opioid toxicity such as miosis, respiratory depression, or an altered conscious state. The officer was monitored at the hospital, did not receive naloxone, and recovered after several hours.

In another incident, four police officers developed adverse health effects while responding to a reported drug overdose in a hotel room. The officers wore short-sleeved shirts as well as gloves and half-facepiece respirators with N100 filters during parts of the response. All four officers experienced dizziness while some also experienced lightheadedness, blurry vision, feeling groggy, and various other symptoms. None of these clinical findings are suggestive of opioid exposure, and none

exhibited the typical effects of opioid exposure, such as miosis or respiratory depression. One officer received naloxone at the scene. The officers were monitored at the hospital for several hours, during which time their symptoms subsided. Based on a limited review of many exposed responders, the absence of actual harm, and the understanding that many drug users and suppliers are dermally exposed to fentanyl on a regular basis, the clinical effects noted are most consistent with the nocebo effect. Response to naloxone in this population is nonspecific, and likely noxious and not pharmacologic in nature.

Dr. Nelson pointed also to the suggestion, and the media have perpetuated the misconception, that carfentanil and other high potency fentanyl derivatives are resistant to reversal by naloxone. However, animal and accidental human exposure data have demonstrated that carfentanil poisoning is readily reversible. But like all competitive antagonists there is a dose-response relationship to naloxone's activity. Concern arises when a very high dose of a fentanyl (or any opioid) is administered, since a commensurately larger dose of naloxone is required to reverse its effects.

Although published evidence is not available to support the caution against using alcohol to clean the skin, theoretically, a carrier such as alcohol could promote absorption of fentanyl through the skin. Additionally, inhalation of aerosolized fentanyl is a concern in a windy environment, but casual exposure during a routine interaction is exceedingly unlikely. The fentanyls are not volatile so ambient exposure is not possible.

The message that touching any amount of fentanyl can harm you, which had been communicated by the U.S. DEA and many law enforcement agencies, is making people unnecessarily fearful. The repercussions of this fear on responders and victims is concerning. Providing a better explanation of concepts such as dose-response, potency, and therapeutic index can facilitate a better understanding of the true risks. Recent federal interagency guidance is more appropriate and helps to dispel the fear: https://www.whitehouse.gov/ondcp/key-issues/fentanyl/

OBJECTIVE FIVE: DISCUSS THE OPTIMAL PRODUCTS, DISTRIBUTION, AND LOCATIONS TO STOCKPILE MEDICAL COUNTERMEASURES FOR RESPONSE TO A MASS CASUALTY OPIOID INCIDENT

Facilitated by Susan Cibulsky, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response

The intent of the session on stockpiling opioid medical countermeasures was to review countries' approaches and discuss goals, challenges, and possible solutions toward optimizing stockpiling strategies. Participants acknowledged the benefits of stockpiling, given the increased risk of a mass exposure opioid incident and the availability of an effective antidote. Furthermore, familiarity and experience administering naloxone to treat opioid overdose is widespread among clinicians, emergency responders, and even some laypeople.

Peter Blain described the U.K.'s approach, Milan Patel explained that of Canada, and Susan Cibulsky summarized activities in the U.S. Each of these three countries has undertaken a recent review of medical countermeasure stockpiling, including current status and required steps to enhance preparedness. Since opioids can be employed as weapons through various mechanisms, multiple types of scenarios have been used to guide the assessments. Feasible worst-case scenarios that could result in hundreds to thousands of casualties address aerosol releases in which opioids are inhaled and contamination of food or water leading to opioid ingestion.

Naloxone is approved and available in vials for injection in the U.K., Canada, and the U.S., as an IN spray in Canada and the U.S., and as an autoinjector for IM or subcutaneous (SC) administration in the U.S. In many local communities, significant amounts of naloxone are maintained and used on a daily basis. Hospitals tend to stock vials and pre-filled syringes, ambulances carry pre-filled syringes, nasal spray, and/or vials, and some community members may carry nasal spray or autoinjectors. In the U.K., Canada, and the U.S., strategies have included federal stockpiles to supplement or backfill local supplies, regional stockpiles, and temporarily pre-positioning medical countermeasures for special events. However, in the opioid mass exposure scenarios, aside from special events with additional pre-positioned supplies, local, immediately available medical countermeasures are likely to be exhausted quickly. Opioids, like most other chemical agents, exert their toxic effects rapidly; initial treatment may be required within minutes. Therefore, central stockpiles will have limited utility in the initial emergency medical response.

The three presenters agreed on the challenges and several recommendations. Due to the need for rapid medical treatment of severe opioid poisoning, adequate supplies of medical countermeasures must be readily accessible to the responder or clinician. A distributed system of "mini-stockpiles" could provide accessible supplies to emergency medical services for use in the field, where easy to administer formulations such as autoinjectors and IN spray may be preferred, as well as to hospital-based clinicians who may prefer to titrate IV dosing using vials. A Boston, MA hospital maintains such a mini-stockpile in their pharmacy. By making a one-time purchase of extra antidote and periodically rotating it into their regular stock, they maintain a fresh emergency cache.

Patients may require ongoing treatment in a hospital setting. A central stockpile can still play an important role by providing antidotes for administration several hours after the incident

and/or backfilling depleted local supplies. Pre-positioning medical countermeasures including opioid antidotes for special events and planned mass gatherings is good practice and should continue to be part of stockpiling strategies.

In a mass exposure incident, an antidote that is longer-acting and higher potency than naloxone could theoretically offer an advantage by reducing the demand for repeated dosing, thereby allowing responders to treat more patients in a given amount of time. Autoinjectors that use a reloadable cartridge system could also provide a rapid and easy means of administering antidote. Additional initiatives to facilitate rapid and effective emergency medical response to a mass exposure opioid incident include: providing adequate training in the recognition of exposure and treatment needs; establishing a registry that documents in real time the antidotes available in a community; and an associated clinical guide with recommendations on antidote use and stockpiling.

OBJECTIVE SIX: DISCUSS THE RESEARCH AND DEVELOPMENT NEEDS FOR OPIOID ANTIDOTES

Facilitated by David Jett, U.S. Department of Health and Human Services, National Institutes of Health

The BARDA Chemical Medical Countermeasure Program – Opioids Medical Countermeasure Development: Kristen Herring, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority

Kristen Herring described the overall mission and recent accomplishments at the Biomedical Advanced Research and Development Authority (BARDA) in developing medical countermeasures (MCMs) for chemical threat agents. Current research interests at BARDA related to opioid overdose were highlighted. Their program is interested in developing drugs that would be suitable for response to a mass casualty incident as well as community use, and include those that target respiratory depression, rather than traditional opioid receptor antagonists. BARDA's objectives are that therapeutic MCMs should be fast acting, long lasting, effective against a variety of opioids (e.g., fentanyl, carfentanil), and amenable for use in a mass casualty setting. Nalmefene for injection (IV, IM, and SC) was previously FDA approved for opioid overdose reversal but eventually withdrawn from the market due to low sales. Opiant, BARDA, and the National Institute on Drug Abuse are currently developing an IN nalmefene product using a proprietary absorption enhancer to generate a fast acting, long duration treatment for opioid overdose. Compared to IM naloxone, this IN nalmefene product exhibits a longer half-life and is five times as potent at the opioid μ-receptor. The new nalmefene product displays a similar Tmax to IM naloxone (15 minutes) but in contrast to naloxone's half-life of 2 hours, nalmefene's half-life is 7-8 hours. BARDA expects that a New Drug Application for IN nalmefene will be filed in 2020.

Are Better Medical Countermeasures Needed? Opioid Medical Countermeasure Research Questions: Milan Patel, Public Health Agency of Canada, Center for Emergency Preparedness and Response

This presentation focused on key questions in opioid MCM research. First, the essential characteristics of an ideal opioid antidote were described. Most importantly, the MCM should be safe and effective (exhibit a large therapeutic index), have an easy and rapid method of administration, and have a clear trigger-to-treat. Of secondary importance are long shelf life, room temperature storage, and broad-spectrum efficacy against opioid compounds. Mr. Patel also compared the challenges associated with the general opioid public health crisis and the health security threat. For example, health security is concerned with various modes of exposures to opioids at relatively high doses after deliberate release with the intent to harm people. The population would mostly be naive to opioids and many casualties could be expected. By contrast, the opioid public health crisis is generally characterized by lower dose exposures of relatively young adults, who have some opioid tolerance, in small numbers or individual cases at a time.

Some unknowns include the optimal dosage form (e.g., autoinjector, nasal spray, other) of MCMs for mass casualty incidents, what is the optimal dose and regimen of naloxone, whether nalmefene is better than naloxone, or naltrexone better than the other antidotes. Finally, several novel approaches to MCM research and development were discussed, including working with compounds that directly stimulate respiratory drive, combined therapies that could be used for opioids or nerve agents which would reduce the necessity of differential diagnosis, and exploring pre-treatment. Canada has a Canadian antidote registry project that is led by the Public Health Agency of Canada in collaboration with other federal and regional agencies. The purpose of the registry is to maintain a database of antidotes stocked throughout the country and a clinical guide to their use.

Medication Development for the Treatment and Prevention of Opioid Overdose - A NIDA Perspective: David McCann, U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse (NIDA)

David McCann discussed the history and development of IN naloxone as a treatment for opioid overdose. An improvised nasal naloxone device has been widely used within the U.S. for large volume, low concentration doses, which is not ideal and not approved by the FDA. NIDA and industry partners supported research on a refined IN naloxone that resulted in FDA approval after it was demonstrated that plasma levels of naloxone, especially during the first few minutes after IN administration, are at least as high as plasma levels observed for the lowest FDA approved dose of parenteral naloxone (0.4 mg, IM). The improvised nasal device uses 1 mL in each nostril and delivers a total of 2 mg naloxone while the FDA

approved IN device Narcan® (Opiant Pharmaceuticals) uses 0.1 mL in one nostril and delivers 4 mg naloxone. Due to the anatomy and size of the nasal cavity, only a relatively low volume of a liquid formulation can be effectively administered, ~100–150 µL in each nostril. Volumes in excess of this amount will not be bioavailable via the mucosal membrane of the nasal cavity due to drug loss anteriorly and posteriorly (out through the nostril or down the esophagus). This affects the pharmacokinetics of the naloxone delivered by the improvised device as less naloxone reaches the circulation. Consequently many more doses of the improvised device are required to reach the same blood level of naloxone as a single injection of IN Narcan®. Other NIDA projects were discussed including IN nalmefene (Opiant), direct respiratory stimulants, and private sector projects such as an 8 mg naloxone nasal spray being developed by Insys Therapeutics.

Medical and Public Health Aspects of Medical Countermeasures for Opioid Threats - the Poison Center Perspective: Lewis Nelson, New Jersey Poison Control Center and Rutgers New Jersey Medical School.

The last presentation in the MCMs session was from Lewis Nelson of the New Jersey Poison Control Center and Rutgers New Jersey Medical School. Here, the expansion of the availability of naloxone for public use was discussed, as well as recommended dosing. For health care providers, several textbooks recommend an initial dose of 0.04 mg IV naloxone. Dr. Nelson also proposed to the audience that naloxone may not be needed for many people with opioid overdose because many are still breathing adequately despite being unconscious, and that control of respiratory depression is the key lifesaving medical intervention in those who are not adequately ventilating (this is quantified as the therapeutic index). This is best done with a bag-valve-mask apparatus or barrier protection for mouth-to-mouth breathing. Withdrawal precipitated by an opioid antagonist in a patient with opioid tolerance and dependence can cause severe, even life-threatening, health effects. Intranasal administration may have certain advantages over IV due paradoxically to its slower onset of reversal of intoxication and precipitation of opioid withdrawal. However, in distinction to intentional users, most victims of a deliberate opioid release will not be opioid dependent and withdrawal is not a concern. This presentation illustrated the nuances in the clinical treatment of patients exposed to opioids.

OBJECTIVE SEVEN: CAPTURE KEY POINTS REGARDING THE CURRENT STATE OF PLAY; RECORD KEY GAPS AND HOW THEY MAY BE ADDRESSED

Facilitated by David Russell, Public Health England

CONCLUSIONS:

- The workshop was a pivotal opportunity for multi-disciplinary information sharing
- Synthetic opioids are easily available from a variety of sources including prescriptions and illicit markets
- Large numbers of new opioid analogues have been synthesized in recent years and can be produced in large quantities
- Fentanyls may be aerosolized, inhaled, and absorbed through the respiratory tract
- High potency, ease of access, and ease of dissemination could result in mass casualties
- Latency to adverse health effects is short, so rapid intervention is required to save lives
- Clinical acumen is the key to successful recognition and intervention
- Rapid access to suitable countermeasures facilitates the management of casualties
- Efficient and effective response requires prior multi-sectoral emergency planning and preparedness
- Crisis and emergency risk communication with communities is critical throughout response and recovery

RECOMMENDATIONS:

- Construct scenarios and hold functional exercises addressing the public health risks of deliberate release of opioids
- Factor poison control centers into emergency planning and preparedness
- Integrate all agencies and organizations with a role to play into emergency planning and preparedness for such eventualities
- Raise public awareness through community engagement programs

CONTRIBUTING AUTHORS

The following people contributed to the writing of this workshop summary:

Susan M. Cibulsky, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response

Danny Sokolowski, Health Canada, Chemical Emergency Management and Toxicovigilance Division

Christine Gagnon, Health Canada, Chemical Emergency Management and Toxicovigilance Division

Lewis S. Nelson, Rutgers New Jersey Medical School, Department of Emergency Medicine

Luke Yip, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

Renee Funk, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

David A. Jett, U.S. Department of Health and Human Services, National Institutes of Health

David Russell, Public Health England, Centre for Radiation, Chemical and Environmental Hazards

Anjali K. Nath, Beth Israel Deaconess Medical Center, Boston, MA, Division of Cardiovascular Medicine

PARTICIPATING ORGANIZATIONS

Health Canada

Public Health Agency of Canada

Defence Research and Development Canada (DRDC)

European Commission, Directorate-General for Health and Food Safety

European Monitoring Centre for Drugs and Drug Addiction Germany, Bundeswehr

Japan, National Hospital Organization Osaka Medical Centre – DMAT Secretariat

Mexico, Federal Commission for Protection Against Sanitary Risks (COFEPRIS)

Public Health England

American Association of Poison Control Centers

American College of Medical Toxicology

Boston EMS

Boston Public Health Commission

Brigham and Women's Healthcare

Harvard University

Massachusetts Department of Public Health

Massachusetts General Hospital

Rutgers New Jersey Medical School, Department of Emergency Medicine

U.S. Army Medical Research Institute of Chemical Defense

U.S. Department of Defense, Defense Threat Reduction Agency

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

U.S. Department of Health and Human Services, National Institutes of Health

U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response

U.S. Department of Homeland Security, Chemical Security Analysis Center

U.S. Department of Homeland Security, Countering Weapons of Mass Destruction Program

U.S. Department of Transportation, National Highway Traffic Safety Administration

Wisconsin's Public, Environmental, and Occupational Health Laboratory