Prescribe to Prevent:
Overdose Prevention and Naloxone Rescue Kits for
Prescribers and Pharmacists

September 2016

TRANSCRIPT

Prescribe to Prevent Title Slide
Welcome to Prescribe to Prevent: Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists.

You will learn from expert faculty, including a prescriber, a pharmacist, and a lawyer, how to educate your patients about overdose prevention and how to prescribe naloxone rescue kits.

Core Topics
Core topics include:
- Risk factors for opioid overdose
- How to recognize and respond to an opioid overdose
- How to incorporate naloxone into that overdose response
- And the medico-legal issues surrounding the distribution of naloxone, including third party prescribing and Good Samaritan laws.

Obtaining Your CME Credit
At the conclusion of the program if you wish to receive CME, CNE, or ACPE credit, you must register in order to take a post-test and complete an evaluation. With a passing score of 70% or greater, you'll be able to print your certificate.

Program Support
This program is provided by Boston University School of Medicine, and is supported by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services.

Educational Objectives
At the conclusion of this activity, participants will be better able to:
- Explain the epidemiology of overdose
- Explain the rationale for and scope of overdose prevention education and naloxone rescue kit distribution
- Incorporate overdose prevention education and naloxone rescue kits into medical and pharmacy practice by
  - Educating patients about overdose risk reduction and

    - Furnishing naloxone rescue kits
- Explain the legal issues around furnishing naloxone rescue kits.

Epidemiology and Overdose Risks
Hi, my name is Alex Walley. I'm a general internist, and an addiction medicine specialist on faculty at Boston University School of Medicine. I take care of patients in Primary Care, where I prescribe buprenorphine, and I take care of patients at a methadone maintenance program. At the Department of Public Health in Massachusetts, I serve as the Medical Director for the Opioid Overdose Prevention Pilot Program. I'm going to start off talking today about the epidemiology of overdose.

Drug Overdose Deaths, 2004-2013
Drug overdose is the leading cause of accidental injury death in the United States, surpassing deaths caused by motor vehicle crashes, and firearms.

Opioid Overdoses
The yearly increases in drug overdoses have been driven by opioids since 2000 with prescription opioids, like oxycodone and hydrocodone, responsible for the increases early on. More recently, since 2010, illicit opioids, like heroin, have surged.

States Affected by Fentanyl Overdose Incidents and Deaths
Increasing numbers of deaths are associated with fentanyl, which is produced illicitly and sold as heroin, or fentanyl that is sold as diverted, counterfeit prescription opioids.

Overdoses
As the leading cause of injury death, overdose is reducing overall survival among Americans. A 2015 study from Ann Case and Nobel Laureate, Angus Deaton, demonstrated that middle-aged white Americans have a worsening overall mortality rate since 2000, whereas people from other countries have had yearly improvements.
This worsening mortality is largely driven by dramatic increases in poisonings, which are mostly overdoses.

Opioid Overdose Costs, 2009
Opioid overdose not only causes deaths; it also costs a lot of money. In a study of opioid overdose in 2009, opioid overdoses cost over $20 billion to society. $2.2 billion were from direct costs for inpatient emergency department physician and ambulance services, and $18.2 billion was connected to indirect costs from lost productivity from absenteeism, and from mortality. The cost to society per opioid overdose was $37,000. By preventing opioid overdoses, and providing access to addiction treatment, there is great potential for saving individual lives, and saving cost to society.

Where Users Obtained Opioids
People using prescription opioids without a prescription most commonly get those opioids from a family, or a friend: the people in their social network. Buying prescription opioids from a drug

dealer, or off the Internet is much less common.

Where Friend/Relative Obtained Opioids
But where do family and friends get their prescription opioids? Not often from the Internet, or from drug dealers. The great majority of friends and family get their prescription opioids from one doctor, and so as prescribers and pharmacists, we have a responsibility to think about what's happening to the opioids that we're prescribing to patients.

Transition from Prescription Opioids to Heroin
Both qualitative and epidemiologic studies have also demonstrated that heroin addiction is often preceded by prescription opioid misuse. A person in the qualitative study titled "Every 'Never' I Ever Said Came True: Transitions from Opioid Pills to Heroin Injecting" explains that when long-acting oxycodone changed its formulation in 2010 to become tamper-resistant, he was triggered to transition to injecting heroin. "I was big into OxyContin at first, and I still used heroin a little bit when OxyContin was crushable, but at that point I only sniffed, and I only did it when I had problems finding OxyContin. It wasn't until the OxyContin switched to the tamperproof versions that I really just went straight to heroin, and immediately started shooting it, which I guess was a little over a year ago."

Opioid Overdoses
A slowing in the growth of prescription opioid-related overdoses has been accompanied by a surge in heroin, and more recently fentanyl-related overdoses. This transition may be due in part to a reduction in the supply, and misuse potential of prescription opioids through the switch over to abuse-deterrent formulations, and more restrictive prescribing practices that started around 2010.

Benzodiazepines and Opioids
Benzodiazepines are an important contributor to opioid overdose deaths. Benzodiazepines are present in 31 percent of opioid-related overdoses. Opioids are present in 75 percent of benzodiazepine-related overdoses. Among people prescribed opioids, the risk of overdose death is 3.8 times higher for people prescribed benzos, also.

How do opioids affect breathing?
How do opioids affect breathing? How do opioids actually cause overdose? Why do victims stop breathing? Opioid receptors are found throughout the nervous system, including:

- the **brain** where opioid receptors in the cerebellum, nucleus acumbens, and hypothalamus control pain perception, emotion, reward and addiction
- opioids dampen transmission of peripheral pain signals through the dorsal horn of the **spinal cord**
- in the **peripheral neurons** opioids bind pain receptors in the peripheral tissues, reducing pain sensation
- in the **intestines**, opioids inhibit peristalsis, which can lead to constipation
- opioids affect breathing in the **brainstem**; opioid receptors in the medulla oblongata control breathing and heartrate. When these receptions are flooded with opioids, the receptors are completely stimulated, eliminating the drive to breathe. Reduced breathing rate is typically

the cause of opioid overdose death.

Opioid Overdose

The drive to breathe stops, because of reduced sensitivity to changes in oxygen, and carbon dioxide levels. There is decreased tidal volume, and respiratory rate. Respirations decrease, leading to a decrease in oxygenation, and then loss of consciousness. When breathing stops, the blood is no longer oxygenated, and the heart and brain will shut down, and the person dies.

This process develops over minutes to hours with most opioids, like heroin or oxycodone. It is not usually instantaneous. Decreased respiratory rate, decreased level of consciousness is accompanied by lower blood pressure, heart rate, and body temperature, and mitosis, or pinpoint pupils. The skin takes on a blue or gray tinge, including the lips, and the nail beds. Note that fentanyl is a more potent, faster-acting opioid than heroin, or oxycodone, and therefore, fentanyl overdoses can evolve more rapidly – in seconds to minutes. Furthermore, it is not detectable in the standard opiate toxicology test, and requires a fentanyl-specific test.

Common Risks for Opioid Overdose

As prescribers and pharmacists, we need to understand the risks of overdose, and convey those risks to our patients. Many of the risks for opioid overdose are well established, and these can be helpful in educating patients. We need to ask our patients, and learn their history to understand what their risks are.

- Higher opioid doses, such as daily doses higher than 50 morphine milli-equivalents, increase overdose risk. Also, changes in dose, or formulations increase overdose risk. People who use heroin are thus frequently at risk due to unpredictable changes in substance purity from, for example, adulteration with fentanyl.
- Polypharmacy and mixing substances contribute to overdose risk, as opioid overdoses commonly involve other substances. Psychoactive medications of particular concern include barbiturates, stimulants, and benzodiazepines. Other medications that can have synergistically central nervous system depressive effects include clonidine, promethazine, and gabapentin.
- We also need to think about people who are socially isolated. Whether they are using heroin or prescribed opioids they are at increased risk of dying from overdose, because if and when they overdose, there is no one there to rescue them. So we need to educate patients that if they are going to use opioids, someone else should be around so that they can respond if they use too much. Isolation is also associated with depression, which is itself associated with overdose.
- We should also consider chronic medical illness, particularly diseases of lung, liver, and kidney that compromise their function. These increase the risk of overdose because they are the organs that metabolize substances and are responsible for oxygenization. Also, mental illness such as depression and anxiety increase overdose risk.
- Patients who have had a prior non-fatal overdose are at increased risk of having fatal overdose, similar to how patients who have had suicide attempts are at increased risk for completing a suicide.
- Patients who have a previous addiction history have increased risk. They are subject to relapse

and are therefore at increased risk of overdose.

- Periods of abstinence should trigger us to educate our patients about overdose. We often think of abstinence as the goal for our patients with addiction and that over the long term it really should decrease their risk of overdose. But abstinence often comes with reduced opioid tolerance, which is actually a risk for overdose. Thus it is important that we educate patients about that. So we are particularly concerned about people who are released from incarceration and patients leaving detox. We also need to think about patients in recovery, and who are abstinent from opioids, and educate them about their increased risk if they relapse.

For Patients: How to Prevent Overdose

Here's some messages that you can convey to your patients, and that they can take home with them: Only take prescription opioids prescribed to you, and take them only as directed. If you have an opioid problem, I can help you find treatment. Make sure your prescribers, and pharmacists know all the medications you are on. Don't mix opioids with other drugs or alcohol.

Be careful, if you miss or change doses, feel ill, or start new medications. Store medication in a safe and secure place, and dispose of unused medications. Abstinence, meaning not taking opioids for a period of time, can reduce tolerance, and increase overdose risk. Teach friends and family how to respond to an overdose, and the role of naloxone in an overdose.

Taking an Overdose History and Delivering Prevention Education

Okay. Next, we're going to talk about taking an overdose history, and delivering prevention education.

Overdose Education and Naloxone Rescue

I want to reiterate the prevention messages that your patients need to know. They need to know that mixing substances, abstinence which lowers tolerance, using alone or being socially isolated, being on a high dose of opioids or getting illicit opioids from an unknown source, chronic medical and mental health illness, or being on longer-acting opioids all increase one's risk of an opioid overdose.

For Prescribers: Assess Overdose Risk

Prescribers should assess overdose risk as part of a patient's history by, number one, reviewing medications, and checking the prescription-monitoring program; two, reviewing medical and social history for above-mentioned risk factors; three, taking a focused substance use history, and four, obtaining an overdose, or over-medication history.

For Prescribers: Overdose/over-medication history

You want to ask directly, and specifically about these issues with your patients. For those patients prescribed opioids, or benzodiazepines, ask, "Have you ever taken enough medication that you were drowsy, and could not wake up?" For patients who are using heroin, you can be more direct, and ask, "Have you ever overdosed?" If the answer in either case is, "Yes," then you want to ask, "What were you taking, and how did you survive?" From there you want to ask "what strategies

do you use to protect yourself from overdose?" Don't forget to ask about medications, and how they keep them safe. "How do you keep your medications safe? Are they locked up and secure?" It's important to ask about locking up medications, because most people who are using prescription opioids not prescribed to them, get them from friends or family.

For Prescribers: Overdose witness history

You want to ask the patient about overdoses that he or she has witnessed. "How many overdoses have you witnessed? Were any fatal? And what did you do? What is your plan if you witness an overdose in the future?" At this point, you want to hit on the specific recognition, and response options that we are going to cover later in the talk. "How do you recognize an overdose? How do you call for help? How do you rescue-breathe? Are you trained in CPR? How do you give naloxone?" Ask specifically about a naloxone rescue kit. "Do you have a naloxone rescue kit? Do you feel comfortable using it?" Understanding the patient's experience, and knowledge should guide the education you provide.

For Pharmacists: Assessing Risk

For patients filling prescriptions, pharmacists should assess overdose risk by reviewing the list of medications, optimizing medication safety, and providing patient education. "Have you checked the prescription monitoring program? Is the patient on multiple psychoactive, or sedating medications? Are these medications coming from multiple prescribers? Are these prescribers aware of all the prescriptions? Is the patient aware of the risks? Does the patient and their family or friends know what to do if there is an overdose? Are they equipped with a naloxone rescue kit?"

Overdose Prevention Interventions

Now, I'm going to summarize and introduce overdose prevention interventions.

Strategies to Address Overdose

There are several existing strategies that improve opioid prescribing safety, access to medication-assisted treatment, and reduce the harms of injection drug use. They include prescription monitoring programs, safe storage strategies, safe opioid prescribing education, opioid agonist treatment, and supervised injection sites.

Prescription Monitoring Programs

Prescription monitoring programs are mandated in most states for prescribers, and pharmacists to integrate into their practice in order to monitor the medications that patients are prescribed by all prescribers. How they can be used best as tools to address opioid overdose needs to be worked out further, but these are powerful tools to help us figure out how to best keep our patients safe, and prescribe responsibly.

Prescription Drug Disposal

Many communities have safe disposal kiosks that are often hosted at local police stations. The Drug Enforcement Administration, or DEA, now also permits manufacturers, distributors,

treatment programs, pharmacies, and health care facilities to become authorized collectors of prescription medications. DEA and local law enforcement continue to host prescription drug take-back events twice yearly when people can dispose of leftover medications.

Safe Opioid Prescribing Educaiton
There is safe opioid prescribing education, which has received substantial support from federal agencies and is also mandated in some states, like Massachusetts, for prescribers to participate in in order to re-license. So here is one example, which is our affiliated online program called "SCOPE of Pain." There is free CME available at SCOPE of Pain, and at Opioid Prescribing.org.

Opioid Agonist Treatment
Let's not forget medication for opioid use disorders, specifically methadone, buprenorphine, and naltrexone, is supported by evidence for increased abstinence, and decreased opioid use. Methadone and buprenorphine treatment are also associated with decreased criminal activity, improved birth outcomes, and less overdose.

Supervised Injection Facility
A public health intervention that has been associated with reduced overdose death rates is supervised injection facilities. Supervised injection facilities are available in parts of Canada like Vancouver, Europe, and Australia. Here, people are able to inject illicit drugs under the supervision of a nurse. They have been successfully implemented with the collaboration of local enforcement, government, and public health leaders, businesses, and people who inject drugs, themselves. The photograph above is from Insight, the Vancouver supervised injection site, which was featured in a *Boston Globe* editorial calling for a supervised injection facility in Boston.

Rationale
We're going to spend much of the remainder of this presentation focused on naloxone rescue kits, as another strategy for addressing opioid overdose. The rationale for overdose education and naloxone rescue kits? Well, first of all, most opioid users do not use alone, so there is somebody, often, there who can help the victim who undergoes an overdose. We know many of the risk factors, which we have already reviewed in detail. There's an opportunity window. Opioid overdose takes to minutes to hours to develop, which means there is time to respond, and help someone. In the case of fentanyl, remember, this window is narrower, like seconds to minutes, because fentanyl is faster acting, and often more potent than other opioids.

The overdose has an antidote, which is naloxone, which can be administered, and restore breathing, and consciousness. Bystanders we know are trainable to recognize and respond to overdose. There's a fear of public safety, specifically fear of being arrested, so in the cases when people don't call for help, it's important to have the tools to address an overdose.

Endorsements for Naloxone Rescue Kits
Naloxone rescue kits have been recognized by several important professional organizations, like the American Medical Association, the American Pharmacists Association, World Health Organization, and American Society of Addiction Medicine…

Strategies and Guidelines

…as well as the Substance Abuse Mental Health Services Administration, which produces, since 2013, this opioid overdose toolkit, which includes descriptions of medication safety, and overdose prevention, including naloxone rescue kits, the Office of National Drug Control Policy, which includes naloxone in its annual strategy, the Centers for Disease Control and Prevention, which recommends co-prescription of naloxone in its 2016 guidelines on chronic opioid therapy, and the Department of Health and Human Services, which recognized increased access to naloxone as one of its three priority areas in addressing the opioid crisis in 2015, along with safe opioid prescribing, and increasing access to medication for opioid use disorders.

Evaluations

Overdose education and naloxone distribution programs have existed since the late 1990s, largely community-based programs that started through harm reduction programs. And so we have a substantial body of research that looks at these programs, and has demonstrated several positive outcomes. Specifically, we have seen multiple feasibility studies in several different populations. There's been increased knowledge and skills of bystanders who can be trained to respond to an overdose, as well as non-medical bystanders, patients, and their social networks. We haven't seen any increase in use in opioids. However, we have seen an increase in drug treatment in a few studies that have looked at this. In several communities there has been a reduction in overdose rates, where the overdose education and naloxone distribution programs were implemented. Overdose education and naloxone rescue kits have been shown to be highly cost effective. In a 2013 published study, where in the best case scenario there was a $430.00 per quality-adjusted life year gained, and in a worst case scenario, $14,000 per quality-adjusted life year gain, which is much less than we see in many accepted medical interventions.

Fatal Opioid Overdose Rates by OEND

In Massachusetts, we have had a widespread distribution in many communities of naloxone rescue kits. However, the rollout was somewhat heterogeneous. So, we had some communities where we had a rapid rollout of naloxone rescue kits, and overdose prevention, and other communities where we did not. We took advantage of this mismatch by doing a natural experiment, an observational study where we compared those communities who had no naloxone distribution to those communities that had low levels of implementation, and to those communities that had high levels of implementation. So, on this slide you can see here in blue communities where there was no naloxone coverage. This was our baseline represented by 100 percent of the opioid overdose death rate. In those communities that had between 1 and 100 per 100,000 people who had naloxone rescue kits: in those communities that had that low level of implementation, we saw a decrease in the opioid overdose death rate by 27 percent here in the dark blue. Then, in the communities that had even a higher level of implementation, meaning greater than 100 naloxone rescue kits per 100,000 people, we saw a further reduction in the opioid overdose death rate, 46 percent. So, this is some strong observational evidence that the distribution of naloxone rescue kits, along with overdose education in the community can result in reduced opioid overdose death rates.

Overdose Rescue and Response with Naloxone

Greetings; I am Jeff Bratberg. I am a clinical professor, pharmacy practice at the University of Rhode Island, College of Pharmacy. I am also an infectious disease specialist Roger Williams Medical Center in Providence, Rhode Island, and a past President of the Rhode Island Pharmacist Association with whom I began implementing pharmacy based naloxone education and opioid overdose prevention programs in the state of Rhode Island along with collaborations at the Department of Health, and actually the Governor's office as well. I am going to talk about overdose rescue and response with naloxone.

How Naloxone Reverses Opioid Poisoning

So first, let's review how does naloxone reverse opioid poisoning from prescription opioids, heroin, or even fentanyl? We have discussed previously how overdose is too many opioids; it causes slowing and/or stopping breathing which is really an overdose at those opioid receptors in the brain. Naloxone goes to those opioid receptors whether they are mu or kappa or delta receptors and disrupts opioids from those receptors because naloxone has a higher affinity for those receptors competing with any opioid found there, removing them and restoring breathing and/or consciousness.

Naloxone Basics

Naloxone takes effect in about two to three minutes. If the patient isn't responding, a second dose may be administered. It is very important when prescribing or dispensing naloxone that at least two doses is dispensed or prescribed. And naloxone, when it is bound to those receptors, it wears off in thirty to ninety minutes. Patients can go back into overdose if long-acting opioids were taken, meaning that the opioids are still around. Patients should avoid taking more opioids after a naloxone administration so they don't go back into overdose after that thirty to ninety minute period when naloxone wears off. Patients may want to take more opioids during this time because they are going to feel symptoms of withdrawal. The shelf life of naloxone is about twelve to twenty four months depending on the formulation. It is important to store it at room temperature to minimize degradation.

Comparison of Opioid Overdose Response Order of Actions (2015)

Let's talk about various orders of actions of overdose response of opioid overdose response. All of these guidances came out in 2015. Now all of these response actions begin with the recognition of overdose: reduced consciousness, respiratory depression, pinpoint pupils, and checking for a response such as yelling their name, shaking them, rubbing the center of the victim's chest with a knuckle. And all of them recommend repeating naloxone administration after that two to three minute period and staying with the patient until help arrives. Now the steps in the American Heart Association guidance is to call 911 after recognizing overdose and checking for a response, to begin CPR, which is rescue breathing or chest compressions, and give naloxone. And if no response after that naloxone, continue CPR for two to three minutes and then repeat naloxone, ending with placing the patient in recovery position and staying until help arrives.

Now the package insert for both FDA-approved products for community administration are silent rescue breathing and chest compressions but retain most of the same actions as the AHA

guidelines. The New York State Department of Health guidance acknowledges that the order of naloxone administration and inclusion of rescue breathing and/or chest compressions will differ based on the setting or the training of the individual. For circumstances where CPR and rescue breathing can be taught, we recommend the AHA algorithm. For circumstances where this is not feasible, such as training patients in a pharmacy, we recommend adherence to the package insert instructions and to review: that is recognizing overdose, checking for response, giving naloxone, calling 911, placing the patient in recovery position, and if no response, repeat naloxone after two to three minutes and stay until help arrives. One other organization for naloxone administration and opioid overdose is from the World Health Organization which is: recognizing overdose, checking for response, placing in recovery position first, then calling 911, performing rescue breathing, giving naloxone, and then if no signs of life, perform chest compressions, and if no response, give naloxone again after two to three minutes. And again, as all of the steps say, stay until help arrives.

Updated Opioid-Associated Life Threatening Emergency Algorithm (ADULT)
The update opioid associated life threatening emergency (ADULT) algorithm for CPR from the American Heart Association again is to assess and activate, check for unresponsiveness, and call for help. Send someone to call 911, get AED and naloxone, observe for breathing versus no breathing or only gasping.

This next step is to begin CPR if they are unresponsiveness or no breathing. If alone, perform CPR for two minutes before leaving to call 911 and get naloxone and the AED. Administer naloxone. Give it as soon as available. If the person responds, they move, they breathe regularly, they moan or otherwise respond, stimulate and reassess them in that case, continue to check responsiveness and breathing until advanced help arrives, which you called 911 for. If the person stops responding, begin CPR and repeat naloxone. If they don't respond after CPR and naloxone, continue to use CPR, use the AED, follow those instructions, as soon as it is available and continue until the person responds or until advanced help arrives.

How to Respond in an Overdose
So the essential steps – there is really about five step: Again, to recognize overdose, call or text 911, if available, for help, administer naloxone as soon as it is available, or rescue breathing, chest compressions, one of those, and then to end with staying until help arrives and placing the patient in the recovery position if breathing to prevent vomiting.

Recognize Overdose
So let's talk about how to recognize an overdose. Call out the victim's name if you know it and rub knuckles of a closed fist over their sternum. Look for signs of overdose – slow or absent breathing, gasping for breath or a snoring sound, pinpoint pupils, blue or gray lips and nails and sometimes the skin will appear blue or gray.

Intoxicated or Overdose?
An important idea to convey to your patients is to distinguish between the patient being just intoxicated or in a true overdose situation. So if they're just intoxicated they may have small

pupils, but in an overdose the same may be true. What distinguishes someone intoxicated versus overdose is really how arousable they are. The just intoxicated person will respond to a sternal rub, but the person in a true overdose will not respond to a sternal rub. That person won't be speaking, where a person who is just intoxicated may have slurred speech, some speech in general. The other important difference between a person who is intoxicated versus in true overdose is how they're breathing. A person in true overdose will have slowed or stopped breathing, a breathing emergency, often less than 8 times per minute. They may be making choking or gurgling or snoring sounds; they may have blue or gray lips or fingertips, evidence of lack of oxygen deliver to the tissues. Whereas, an intoxicated person is still breathing. They're just drowsy and usually breathing at a rate more than 8 times per minute.

So for the person who is intoxicated, stimulate them but observe them. The person in overdose requires naloxone, rescue breaths and chest compressions depending on the ability of the responder.

Overdose Education and Naloxone Rescue

What your patients need to know about overdose education naloxone rescue is to start with prevention: avoiding mixing substances; be cautious in patients who have abstained from opioids and have low tolerance or no tolerance; those using alone; those using opioids from an unknown source; who have chronic medical diseases; and/or are using long acting opioids because they last longer. Recognition is essential. Unresponsive with slowed breathing. Blue lips. Pinpoint pupils. And what to do are those steps – calling 911 for help or texting 911, administering naloxone, giving rescue breaths or chest compressions, placing the patient in a rescue or recovery position and staying until help arrives.

Call/Text 9-1-1 for Help

Once you have identified the overdose, you need to call or text 911 immediately or tell your patients to do that or send someone to call or text 911 if you are unable to at that time. That medical help is crucial to saving lives. When you talk to the 911 operator, it is important to report that someone is unresponsive and not breathing or struggling to breathe, and to give a clear address and location. Calling 911 as soon as possible improves survival.

Administer Naloxone

The next step is to administer naloxone. There are several demonstration videos to review yourself and we strongly encourage you to share these videos with your patients and patient caregivers.

Rescue Breathing

One of the steps in overdose response is to provide rescue breathing or chest compressions, to the ability of the rescuer. These are steps to teach patients, family, friends, and caregivers. What is happening in an opioid overdose is the person is not oxygenating their brain. They are not delivering oxygen and thus breathing is impaired. So you need to make sure that their airway is clear, placing one hand on their chin, tilting their head back to open the airway, pinching their nose closed, and give two slow rescue breaths into their mouth placing your entire mouth over the

patient's mouth. Make sure the chest is rising. That is why it is important to pinch the nose and open the airway. You must have as clear a path as possible for your breath to get into their lungs. Give one breath every five seconds until they breathe on their own. And if they are still unresponsive, and you have naloxone, it is important to get it out and administer it if you hadn't already given it. If the person is unresponsive and the person knows CPR, like the guidelines from the American Heart Association, and the World Health Organization, give fast and deep chest compressions in addition to rescue breathing.

Stay Until Help Arrives

Once naloxone is administered and if chest compressions or rescue breaths have been given, naloxone is just going to dislodge whatever opioid the patient had overdosed on from those receptors. So the victim still needs oxygenation. So continue rescue breathing, if able to, one breath every five seconds until emergency responders arrive. After two to three minutes, if the patient is still unresponsive, still not responding to sternal rubs, still with slow or no breathing, and perhaps not responding to chest compressions if those are being administered, another dose of naloxone can be given after two to three minutes.

Never leave the victim alone. Whether the person is responsive or not, the person took a long acting opioid such as oxycontin, methadone or extended release morphine, and they can definitely go back into overdose after the naloxone when it wears off. The first thing the person wants to do is to take more opioids because of those withdrawal symptoms. So staying with the patient is also important to make sure that they don't do this and risk going into another overdose.

Stay Until Help Arrives: Rescue Position

If the responder has to leave at any time, for example to call 911, get naloxone, get more naloxone, place the patient in the rescue or recovery position. And you see in the graphic, put them on their side with their top leg and arm crossed over their body. This helps prevent or reduce incidents of choking or vomiting in that patient. And those are symptoms of precipitated opioid withdrawal syndrome.

Naloxone Rescue Kits

Now let's talk about naloxone rescue kits themselves: how to prescribe them, stock them, fill them or dispense them, and how to bill for them.

Naloxone Prescribing Summary

Naloxone rescue kits need to be prescribed to people who are at risk for overdose. Some of those risks we reviewed already – opioid combinations with alcohol or benzodiazepines, opioid doses above fifty oral morphine mill-equivalents per day, purity changes (we have seen an epidemic of fentanyl-contaminated heroin or counterfeit fentanyl pills), anyone with a previous opioid overdose is at extremely high risk, those who are socially isolated, those who have a substance use disorder whether it be alcohol or other substances, anyone who has gone through a period of opioid abstinence, whether in a treatment program, those who are incarcerated or those who quit

using, and patients with chronic medical conditions or mental illnesses that put them at increased risk of overdose. Importantly as you review risk factors with your patient; these and others, if you're also in a state that permits third party prescribing: a majority of the states prescribe to friends and family of people who are at risk of overdose and train them on how to recognize overdose and administer naloxone for those loved ones.

Naloxone Conversation Starters

So to start the conversation, whether a prescriber or perhaps especially a pharmacist who has the ability to recommend naloxone to these patients at risk, you can start with several different conversations. One could be: "opioids can cause bad reactions that make your breathing slow or even stop. This can happen if your body can't handle the opioids you take that day or if you take opioids without alcohol or other drugs. Naloxone is a lifesaver just like a seatbelt or a fire extinguisher." Everyone needs to have it if they are at risk. Another conversation starter could be: "these medications can be helpful but have a range of side effects, like slowing down or even stopping breathing completely. Naloxone can help if this happens by restoring breathing." "Opioid medications increase the risk of breathing emergency with a person who takes the opioid and anyone in their household. Naloxone is needed in case of emergency." This could be directed at people who live in homes with young children who are also at risk if opioids are also in that home. In fact, another conversation starter could be as simple as, "let's keep you and your family as healthy as possible with these medications n your house. Just in case, get naloxone."

Comparison of Products

There are several different forms of naloxone available as of August 2016. There are branded products and there are generic products. Two products are FDA-approved for layperson use. That is Narcan™ nasal spray, and Evzio™ auto injector device. For three of these products there is experience from lay people. The multi-stepped intra-nasal generic, the injectable syringe and vial intra-muscular, and the auto injector branded product. The injectable generic and the intra-nasal multi-step generic do require assembly. And in fact, the glass vial that is used in the multi-step intranasal is also fragile. Now the advantage to the generic products is that you can titrate the dose. You see the strengths that are listed there. Each of these comes either prepackaged in the kit with two devices or needs to be assembled into a kit. You see the cost per kit; the costs vary dramatically between states and between providers but you see a comparison of which ones are relatively more expensive or less expensive than each other.

Prescription Examples

On this slide we see an example of a prescription for the four different types of naloxone: the multi-step intranasal, the intranasal device, the intramuscular naloxone, and the naloxone intramuscular auto injector. We'll have those prescriptions available for you to print out and use in your practice.

Ordering Information

The ordering information is on your screen there. I won't review all of the fields but you see that the multi-step generic again is the glass syringes and a no NDC, there is no code for the atomizer –

it is durable medical equipment. The intranasal branded is manufactured by Adapt Pharma. The auto injector brand is manufactured by Kaleo. And there are at least three intranasal generics as of this recording. It comes in various quantities. There is the customer service numbers and the NDC is there. You will see on the bottom how themucosal atomizer devices come, why they are used, and how to order them from various wholesale manufacturers. Again, it is durable medical equipment.

Naloxone: Billing

Naloxone co-prescription and naloxone recommendations require sustainability in terms of payment. And a growing number of public and private insurers cover at least one naloxone formulation for patients. Insurance coverage for third party prescriptions, which again a majority of states permit by law, is also evolving. Regardless if they are the patient or they are someone who is a caregiver, patients can with insurance coverage pay a copay plus or minus the mucosal atomizers or syringes that they are filling, vials, the intramuscular vials with syringes and needles. So if you are prescribing naloxone, patients without insurance can buy. And again, the cash payments vary widely by state and which formulation is either available in the pharmacy or available by the wholesaler. The intramuscular syringe is over the counter but states vary in the ability and quantity for purchase. So it is probably best for prescribers to put the syringes and needle size on prescriptions for patients. The mucosal atomizer devices currently cost about five dollars each. It can be billed as durable medical equipment but there is no NDC, so the patient usually has to pay for at least those mucosal atomizer devices.

Naloxone Distribution Models

There are several different naloxone distribution models in the United States. We are going to review their prescription specifications, the targeted at risk populations, and the geographic reach. So community-based naloxone distribution is the oldest form of naloxone distribution. A prescriber issues the prescription via a standing order. If medical professionals are required varies by state. Maybe a health department. Maybe a prescriber. These recipients are individuals served by the community-based organization. And the target risk population is the people at highest risk usually. People who use drugs or misuse drugs, prescription opioids or heroin, who can access that community-based organization. And importantly, majority of states now permit prescriptions to be written for third parties: friends, staff of organizations that provide services to individuals at risk of overdose, as well as the person at risk of overdose. The geographic reach is limited to where the community-based organizations are located and operate.

When we look at the model of traditional prescription, this is available in fifty states. So the prescriber is issuing the prescription; the prescriber requires a pharmacist to fill the prescription; the recipients are the patients that the prescriber knows; and the target risk population are people who use drugs and in the care of the prescriber, or people who are in treatment and visiting a prescriber. So for example, someone who is prescribed buprenorphine could be prescribed naloxone as well, because they may be in a better position to respond to overdose considering their history and the people that they may know. Of course, naloxone should also be co-prescribed for opioids exceeding 50 morphine milligram equivalents or opioids and benzos prescribed together. Those are people who are at higher risk of overdose that can be co-prescribed naloxone. And the geographic reach is really all the patients of that particular

prescriber.

A collaborative practice agreement, or CPA, is issued by a non-pharmacist prescriber. The professionals required are a prescriber and a pharmacist. The recipients vary by state. Again the target overdose population is people who use drugs, prescription opioids or heroin, who visit a pharmacy, for example, to purchase syringes to inject; it could be patients who fill a prescription for opioids at a pharmacy who are at risk of overdose. And those risks we have reviewed and would be part of that CPA. So how to identify the patient and recommend naloxone for them. The reach is really any participating pharmacy or pharmacy chain within the state.

A standing medication order is a little bit different than a CPA but has some of the same characteristics. A non-pharmacist prescriber issues it. A prescriber and pharmacist are required. Anyone meeting the criteria specified are potential recipients. And again, people who use drugs who visit a pharmacy, or people filling opioids or prescriptions for opioids at a pharmacy, who can be recognized as those needing naloxone.

A protocol order is really only different than a CPA or a standing order by who issues a prescription. It is issued by a licensing board and only a pharmacist is required. The licensing board sets the criteria for the recipients and again, people filling prescriptions for opioids or people who use drugs who visit pharmacies.

Pharmacists can also prescribe directly. The pharmacists here is directly issuing the prescription. Only a pharmacist is required and they choose the patients: anyone for whom the medication naloxone is indicated. And again, only limited to where the pharmacist practices.

Legal Environment

Hi, I am Cory Davis. I am a Deputy Director of the Network for Public Health Law, a national non-profit that provides legal technical assistance on the ways in which law and policy can be used to improve public health. My work specifically focuses on laws and policies that affect the health and safety of people who use drugs as well as their friends and family members.

Question
Corey, it seems like there's a lot of questions and misperceptions about the legality of prescribing and dispensing naloxone. Can you walk us through the basics?

Naloxone Legal Overview
Sure, great question. The most important thing to understand is that the legal environment for naloxone prescribing is, in general, no different than the legal environment for prescribing any other prescription drug. Naloxone isn't a controlled substance. So none of the laws and regulations governing controlled substances apply. Anyone who can otherwise prescribe which often include nurse practitioners and physician assistants, can prescribe naloxone. It is a generic drug that has been on the market for more than forty-five years. So naloxone can be prescribed to your patient exactly like any other medication. The general liability risk of prescribing naloxone is no higher than any other drug. In fact, because it is a pure opioid antagonist with no abuse potential, the liability risk is probably even lower than with many other medications, such as opioids. We recently published research showing that there hasn't been a single case as far as we can find where outpatient naloxone prescribing dispensing was the grounds for a lawsuit. Further, as I will describe, most states have actively encouraged clinicians to prescribe naloxone by providing additional liability protections for prescribers, dispensers and administrators. Most states have also changed their laws to permit naloxone to be prescribed outside of the traditional clinician patent relationship, for example to a friend or family member of a person at risk. Most states also permit naloxone to be dispensed by pharmacists without the patient first seeing prescriber, through a variety of means. I will go over that in more depth in a minute.

General Prescribing Considerations
The general considerations for naloxone prescribing are no different than any other prescription medication. As an overview, just like with any other medication, the naloxone prescription must be written in good faith in the usual course of professional practice for a legitimate medical purpose. All of those terms are pretty self-explanatory. It basically means that the prescriber must believe that, in his or her professional medical opinion, supported where relevant by peer reviewed literature and expert opinion, that a particular medication is indicated for a particular condition and a particular patient. A naloxone prescription issued for a patient at risk of overdose clearly satisfies all three criteria.

Prescribing Best Practices
As with any medication, following best practices will reduce any potential risk associated with naloxone prescribing. As a prescriber, you should make sure that the patient understands how to identify an opioid overdose so they will know when to use the medication. You also want to make sure that they understand how to administer naloxone, which might include a discussion of the pros and cons of the different formulations. You also want to discuss the risk of side effects, particularly precipitated withdrawal, and the importance of calling 911 after naloxone is administered. And you should consider discussing with the patient other ways of reducing opioid overdose risk. These are all things that should also be covered if the pharmacist provides counseling or consultation to the patient.

Review of Legal Environment

So let's review the general legal background. The important thing to remember is that prescribing naloxone is no different than prescribing any other medication. Nothing that a clinician does is without some liability risk but naloxone prescribing is no riskier than any other medication and probably lower than many. As we will discuss in a bit, many states have also taken action to further reduce any potential liability risk. The outpatient prescription naloxone is a mainstream practice supported by the American Medical Association, the American Pharmacist Association, the American Society of Addiction Medicine, and many others. As I noted, we haven't found a single case in which the outpatient prescription or dispensing naloxone has been the basis of a lawsuit. Of course, as with any medication, you should ensure that the patient understands when and how to use naloxone.

Question
Corey, if I have a patient whose son is coming home from rehab, and who is worried about his overdose risk, but she herself doesn't have any overdose risk, can I prescribe a naloxone rescue kit to her?

Third Party Prescribing
What you are asking about is called third party prescribing. Can you prescribe naloxone to a third party – that is someone who isn't themselves at risk of overdose so that they will have naloxone available to use on someone else.

As you know, in traditional medical practice, you have a three step process. The medical professional examines the patients, diagnoses the patients, and then prescribes the medication that is indicated for that condition and that patient. In third party prescription, the clinician skips the first two steps, generally relying on the report of a person with whom he or she has a professional relationship to determine that naloxone is appropriate for the third party.

This is important because often times the person who is themselves at risk of overdose is not the person who comes in contact with the prescriber. There are a number of reasons for that. The person at risk might be uninsured or underinsured. It might be just be difficult to get an appointment or they might feel stigmatized or ashamed. But for whatever reason, often times it is not the person who is at risk that comes in contact with the prescriber; rather, it is a friend or family member or loved one who is concerned about them.

To address this problem, most state legislatures have taken action to increase the universe of people to whom the prescriber can write the prescription for naloxone. These laws vary a little bit by state but essentially, they wave that general requirement if the physician or other prescriber and the person for whom the medication is prescribed have a provider-patient relationship. In the state that has one of these laws, the legal risk of prescribing for a third party is no different than the legal risk of prescribing naloxone for use on your own patient. It is just expanding that group of people for whom a legitimate prescription can be issued and it is going to vary a little bit by state but typically, the actual prescription is written in the name of the patient, not the name of the person at risk. In most cases, it is not necessary that you even know the name of the person for whom the medication is intended. The prescription is just in the name of the person to whom

it is issued.

Third Party Prescribing: Example Language
I put up a slide of example language of what one of these laws looks like so you can see how simple it is. It just says that a practitioner acting in good faith and exercising reasonable care, which is just a general prescribing requirement, may directly or by standing order prescribe an opioid antagonist to person at risk of overdose as well as a family member, friend, or other person in a position to assist a person at risk of experiencing an opioid-related overdose. You can see that this particular law also removes civil and criminal liability for the practitioner who issues the prescription. As I will touch on in a minute, most third party laws have a similar provision.

Question
Corey, can someone get naloxone directly from a pharmacist, without seeing a physician, nurse practitioner, or physician assistant?

Pharmacist Practice
Another great question. In an increasing number of states it is possible to receive naloxone from a pharmacy without first seeing another medical professional. There are a few different ways that this is possible. In a handful of states, some or all pharmacists are committed to prescribe naloxone on their own authority. Typically, they have to complete some sort of training in order to prescribe naloxone. Some pharmacists who work for the federal government have prescribing authority as well. In about eleven states, it may be possible for a pharmacist to dispense naloxone under a collaborative practice agreement with a prescriber. In practice though, this only happens in a handful of states. By far, the most prevalent means of increased pharmacy naloxone access is through a standing order. It is legal for pharmacists to dispense naloxone via a non-patient-specific standing order in at least thirty-four states. The number has been increasing every year. I am going to go over this more in just a minute.

Collaborative Practice
First, pharmacist collaborative practice, where the pharmacist and the prescriber – typically but not always a physician – work together to manage a patient's medications. There is a large amount of variation between states with regarding the details of collaborative practice agreements. In all states, there must be a written agreement between the prescriber and the pharmacist that sets up the duties and responsibilities of the pharmacist. In the naloxone- specific context, we have seen successful implementations of these collaborative practice agreements in several states. The billing and reimbursement rules vary by state and by payer; that's no different than with any other drug.

Standing Orders for Naloxone Dispensing
The majority of naloxone that is dispensed from pharmacies without a prior prescription is dispensed via standing orders. Another way to think of these is non-patient specific orders. Instead of writing a prescription for a specific patient, the prescriber authorizes naloxone to be dispensed to any person who meets criteria permitted by law and specified by the prescriber, which can be as broad as any person at risk of overdose or might be in a position to assist a person

at risk of overdose. The standing order should be written and it should be clear as to who it covers, what it authorizes, any reporting requirements, and any other important information. There are good examples of standing orders online at prescribetoprevent.org. Many major pharmacy chains now dispense naloxone via standing order in states where it's permitted by law. And as of July 2016, officials in three states, Maryland, North Carolina, and Pennsylvania, have issued standing orders that permit naloxone dispensing by essentially any pharmacist in the state.

Question
How does community-based distribution – meaning naloxone rescue kits that are distributed outside of a medical setting – how does that work?

Community-Based Distribution
At some level you have the same problem with people accessing pharmacists that you have with them accessing prescribers. Just like how many people high risk don't see a doctor, many are also not going to go to a pharmacist, but they might have regular contact with some other organization like a needle exchange program or a social service agency or even a drug treatment program. So being able to reach those people where they are at is really important. In recognition of that fact, seventeen states have now modified their laws to permit standing orders to authorized people or organizations who aren't otherwise authorized to dispense drugs to distribute naloxone. There is variation between state laws but in general, where the law permits the practice, the liability risk to the prescriber is no different than with traditional prescriptions. That means if the prescriber is given an additional immunity for prescribing in the traditional setting, that immunity typically also applies to standing orders that authorize community dispensing. As with all such orders, the specifics are set with the prescriber within the bounds of the law, and he or she is ultimately responsible for the actions of the people acting under the order. This practice is rapidly expanding. The CDC reported that as of 2014, over one hundred fifty thousand people had received naloxone through community distribution channels.

Question
One of the things that I hear a lot about is some providers are worried about legal liability. Can you talk more about how these laws address that?

Addressing Naloxone Liability Concerns
Absolutely. That is a concern that I hear as well. Luckily, it is a concern that was also heard by legislators. And most of the states that have expanded naloxone access have accompanied those expansions with liability protections. Those protections vary by state but in most states, they are very broad making it essentially impossible to win a lawsuit alleging that the person was harmed by naloxone prescribed or dispensed by a medical professional unless, in layperson terms, a medical professional did something very wrong. That means that in these states, the liability risks associated with prescribing or dispensing naloxone are lower than with any other drug. Forty-one states also provide civil immunity delay administrators, which can encourage organizations like social service agencies to feel comfortable having naloxone on hand where the law permits it and administering naloxone in an emergency.

Overdose Good Samaritan Laws

Of equal importance, I think, are what are referred to as overdose Good Samaritan laws. The reason for these laws is that there is good peer-reviewed research as well as a lot of anecdotal information that overdose by standards often times don't call 911. They don't want to risk getting arrested by responding officers. And in many jurisdictions when you call 911, an ambulance is dispatched and police officers are dispatched as well, particularly if you report that there is an overdose. The Good Samaritan law is intended to encourage overdose bystanders to call 911 or to otherwise summon emergency first responders by providing limited criminal immunity to the person who makes the call and typically also the overdose victim. The particulars vary a little bit by state but in most states, the immunity is limited to relatively minor crimes, although some laws also provide protection from probation and parole violations. In all states, the person making the call must actually have the goal of summoning first responders to provide emergency overdose response.

The important thing to remember with these laws is simply that they exist and to make sure that the person you are prescribing naloxone to knows that they exist. This is because it is important that after naloxone is administered that the person who administered it calls 911 so that the victim can be evaluated and treated further if necessary. It is also important to educate law enforcement officers about these laws so that they don't inadvertently arrest people who should have immunity under them.

One of the interesting things I found in my work around these laws is that by and large law enforcement officials support them. In North Carolina, for example, the Good Samaritan law was recently championed by the state sheriff's association. You can also see on this slide, quotes from two law enforcement professionals who are supportive of Good Samaritan laws. I think law enforcement is increasingly understanding that the problem of drug abuse, misuse, and overdose isn't something that we can arrest or lay out of; it is primarily a public health problem that needs a public health response. Law enforcement officers and officials increasingly seeing themselves as part of that public health solution.

Naloxone Access Laws, 2016

This last slide is a visual representation of the state of the laws throughout the country regarding naloxone access and Good Samaritan. This is up to date as of July 2016. You can always see the most current version at pdaps.org. I should note that everything in this presentation is intended to be informational. It is not legal advice. If you have a specific question, please contact an attorney in your state. That said, I am always happy to answer general questions about the laws in any particular state. My email address is available in the course materials.

Thank you for participating in Prescribe to Prevent: Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists. You can receive CME, CNE, or ACPE credit for this activity by completing a post-test with a score of 70% or greater, and an evaluation.