INTRODUCTION TO OPIOIDS

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[Video transcript]

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- [Tia] Hello everyone. Thank you for joining us today. My name is Tia Babu and I am an infectious disease physician at the University of Rochester, Rochester, New York and the New York State STD Center of Excellence. I am here today to introduce Dr. Alicia Lydecker who will be presenting a learning module entitled "Introduction to Opiates." Dr. Lydecker is an emergency medicine physician and medical toxicologist. She completed her residency and fellowship training at the University of Massachusetts and is now working at Albany Medical Center in Albany New York. Currently Dr. Lydecker is interested in the regulation and toxicology of herbal supplements, which despite being natural can still be toxic. Collaborating with national leaders in synthetic chemistry at the University of Mississippi, she has worked on the interpretation of novel metabolites in the herbal supplement, kratom. She also is studying best known consequences of drug overdose including compartment syndrome. Dr. Lydecker has additionally written multiple books chapter- book chapters and presented abstracts on medication safety and adverse event monitoring at national conferences. Without further ado Dr. Lydecker.

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- [Alicia] Thank you very much for the introduction. I'm honored today to give you guys a talk about an introduction to opioids.

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I have nothing to disclose.

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Our learning objectives today are to appreciate the similarities and differences between opiates and opioids; to understand the acute chronic, common, and uncommon adverse effects of opioids; and to recognize signs and symptoms of an opioid overdose and understand how to treat appropriately.

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As a general outline and roadmap here, I just want to kind of show you how we're going to go about this talk- just because there's a lot to cover. First I'm going to start with some definitions of opiates and opioids, and give a distinction between the two. Then we're going to move on to the history of opioid use and how that came to lead to the opioid epidemic. Then we'll discuss the pharmacology of this class of medication or drugs, their clinical effects, how to diagnose opioid toxicity and how to test for it. Then we'll move on to the treatment of toxicity and addiction. And then lastly we'll touch on opioid withdrawal.

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So a very basic concept is understanding what an opioid is.
Opioids or anything that bind to the opioid receptor to produce an effect. This can be anything naturally occurring, semi-synthetic, or fully synthetic. That means these substances can look very different. But as long as they possess the capability to bind to the receptor and produce an effect, it counts as an opioid.

So this is the poppy plant also known as papaver somniferum. Opium is a naturally occurring opioid that is derived from the poppy plant and natural opium contains 0.5 percent codeine and 10 percent morphine.

Remember this scene from The Wizard of Oz where the main characters fall asleep in the poppy field? I don't think that was a coincidence.

So an opiate is anything derived from naturally occurring opioids in the poppy plant. This include opium, codeine, and morphine. An opioid on the other hand, includes anything that is opiate like, meaning anything that acts on the opioid receptor. That this can include naturally occurring opiates. But it also encompasses the semi-synthetic or fully synthetic substances as well. This would include heroin, oxycodone, hydrocodone, fentanyl, buprenorphine, methadone, meperidine, and so forth.

Without going too in-depth into organic chemistry and chemical structures, all you need to do is look at the structures I have here. And you can see that the opiates on the left look very similar to each other. And they look entirely different from the synthetic opioids to the right. This will be important again when we discuss urine drug screening.

To understand how we got to where we are today, we have to take a look at the history behind opioid use.

Opioids were first referenced in ancient Sumerian tablets dating back to 4000 B.C. The euphoric effects produced by the naturally occurring opiates were evident in the name which the Sumerians gave the poppy plant; they called it the joy plant.

The Ebers Papyrus is the oldest medical text known and it comes from ancient Egyptian times. This text recites how the poppy plant was useful for soothing crying children. While it may be effective, we certainly don't recommend that indication today.
Now trading brought opium to ancient Greece. During this time it was referenced commonly in mediums such as books, statues, legend, and myth. Poppy pods are depicted in this particular carving. It said that the term opium comes from an ancient Greek word "opus", meaning something along the lines of sap. To produce opium, the poppy pot is sliced after the flower petals fall off. And a milky white substance containing a psychoactive substance is obtained.

That milky sap is seen here on an opium pot - sorry, on a poppy pod.

So from Greece, opium use continued to spread eastward. Thanks to the British East India Company, it was brought to China where its use flourished. It was commonly consumed in opium dens, in the picture here.

Opium was banned in China, and tensions with Britain, primarily over trading, ultimately led to opium wars. The Chinese were defeated in both wars.

With gold rush of 1848 brought many Chinese immigrants to the United States, along with the tradition of opium dens. This led to an upswing in opiate use which was still legal and available without a prescription at the time.

In 1874, a London chemist boiled morphine with acidic anhydride, which is a substance similar to vinegar, and synthesized heroin. Bayer, of their aspirin, claimed this to be a non-addictive analgesic and good for coughs, bronchitis, and tuberculosis. The addictive power of opiates soon came to be recognized - most notably, opium and heroin - sorry - opium and morphine, because they had been around longer. To combat this issue, the Harrison Narcotics Act was enacted in 1914, which made non-medical opioid drug use illegal. With all the scrutiny on morphine and opium, the heroin subculture began to form about the same time. Physicians could be granted a prescribing license, but enforcement was strict, and over a span of 20 years, 25,000 physicians were reported in violation for reasons including prescribing to those with addiction. Popularity increased. But ongoing legislation continued. Heroin wasn’t made illegal until the 1920s. Despite this, use of heroin and subsequently other opioids has continued.

Modern prescription opioids began being introduced in the 1970s. There was hesitancy surrounding them. Given the stigma of morphine and heroin had gained. A few publications helped to reverse the stigma by reporting low rates of addiction, including this letter published in The New England Journal of
Medicine in 1980, stating the development of addiction is rare in medical patients with no history of addiction.

So this starts to set the nation up for the now infamous opioid epidemic.

So how did we get to where we are today? Rates of opioid prescriptions have continued to rise, not only because of articles claiming low addiction potential, but also because many organizations shifted emphasis onto the importance of pain control in patients. You may have heard of the concept, "pain as the fifth vital sign," which was introduced at a meeting in 1995. Prescription opioids were also heavily marketed during this time and new formulations, which were longer acting but potentially more addictive, were released. Increased prescribing led to increasing amounts of tolerance and drug dependence. For many this was a major problem by itself. For others, prescription opioids were a gateway to heroin, whether it be due to loss of efficacy of the prescribed medication, lack of sustained access to the medication such as a physician no longer providing scripts or just plain curiosity. In more recent times, something called the Dark Web has been a contributor to the nation's health crisis. This is a network of websites which are accessed through a special software and essentially untraceable. This has added fuel to the fire as anybody with a computer can go online and order whatever substances they desire without any regulation. Another important aspect of the epidemic is fentanyl and fentanyl derivatives. This is a synthetic opioid 100 times more potent than morphine, which has made its way into the heroin supply has even sought after by some. We'll see in a second how this has impacted us.

So this is a graph released by the CDC showing rates of opioid pain reliever deaths in comparison with rates of treatment admissions for opioid addiction, in addition to sales of opioid pain relievers. We can see that over time, the rate of prescriptions, or the rate of sales of these opioid pain relievers has steadily increased. But the important aspect of this graph that I want you to, kind of take home as take home message is that, with the sales, that the sale- the rate of sales increasing, the rate of addiction and debts has essentially mirrored that.

66.5. This is how many opioid prescriptions were written per 100 persons in 2016. This is down trending from prior years but it is still an astonishing number.

Looking at mortality data, the overall number of people dying from drug overdose has been steadily increasing over the years. As of 2016, 144 people die every day from a drug overdose. That's more than firearms or motor vehicle accidents. I want you to take note of the sharp uptick in the last year or so.
So this is a graph looking at the age adjusted rates of drug overdose death—drug overdose deaths by specific substance. That sharp uptick that we saw on the prior image is likely explained by the dramatic increase in deaths due to heroin, represented by the solid blue line, and synthetic opioids which include fentanyl—the dotted orange line. You can see the number of deaths due to fentanyl has more than tripled over a period of two years or so. Sometimes the users will seek out fentanyl, but often it is mixed in with the heroin, and they are unaware, making a usual dose lethal.

To give you another idea of how much impact the opioid epidemic has made, this is a visual representation of the number of deaths that came from drug overdose in 2015. Each person figure represents one thousand deaths. Yellow figures represent those deaths due to opioids. And again, the data is usually lagging, you know, in terms of how recent it is. So we know that in 2016 there were 12,000 additional drug overdose deaths. And the majority is undoubtedly due to opioid overdose.

The death and addiction are not the only consequence of the epidemic. It’s well known that blood borne pathogens are spread by needle sharing, which is common in those with heroin or other injectable illicit opioid abuse. About one in 10 new HIV infections are due to needle sharing. The good news is that this has been on the decline, in part to needle exchange programs. However the decline has been disproportionate, and the same rate has not been experienced across the board. This is partly due to differences in rates of injection drug use and frequency of sterile needle use. As you can see looking at the graphic depicted here, between 2005 and 2015 there was an increasing proportion of the White population with new I.V. drug use, and a decreasing proportion of Hispanic, Latino, and Black populations.

So hepatitis C is another blood-borne chronic illness associated with intravenous drug use and needle sharing. With the rise in popularity of heroin, we've seen a concurrent increase in the incidence of hepatitis C, notably in the young adult population. On this image you can see those young adults as, you know, the highest kind of line all the way on the right—just the purple line—representing 20 to 29 year olds. Right below that is an increasing rate in the 30 to 39 year olds. And we see a little bit in the 40 to 49 and 50 to 59, but it's really the younger population that is disproportionately having a higher incidence of hepatitis C as the years progress.

So I want to shift gears and help you to understand why the current epidemic is being called a public health emergency. To start, we're going to review some of the pharmacology behind these drugs.
Opioids can be administered by virtually any route, making them a very, very versatile class of medication. This can range anywhere from taking them orally, applying patches to the skin, sucking on drug-infused lollipops, rectal insertion, injection and so forth.

As mentioned before, the way these medications work is by binding to the opioid receptors to produce an effect. There are three main types of opioid receptors- each with varying effects. The mu receptor is responsible for your classic opioid effects, including respiratory depression, meaning slowed or absent breathing, itching, constipation, analgesia or pain control, sedation, and euphoria- or a pleasant feeling. The kappa receptor is also partially responsible for analgesia. It can decrease pupil size and cause adverse psychiatric effects. But it's not associated with respiratory depression or constipation. Less is known about the delta opioid receptors. But they appear to be involved in analgesia, cough suppression, and modulation of dopamine in mu receptor function. Typically, all three types of opioid receptors are involved with each opioid drug. But the extent to each one varies. There are also endogenous opioids which you may be familiar with, if you've ever heard of a term like runner's high. These are produced by the body itself and another class of receptors are associated with these. However for the purposes of this talk, I'd like to focus on the exogenous opioids.

A variety of clinical effects can be seen with opioids as a class. But there are also some unique adverse effects specific to individual drugs.

To help conceptualize I've broken the effects down, to common effects in the setting of therapeutic use, the vaccine in acute overdose situations, chronic effects from long term use, and effects specific to particular opioids.

Let's start with the common acute effects experienced at therapeutic dosing. These medications are often taken for these reasons. And it includes analgesia, which again is pain control, sedation, cough suppression, and euphoria or a pleasant feeling. The negative common side effects include itchiness or nausea and vomiting.

In the acute overdose setting, we see the classic opioid toxidrome, which is the hallmark of opioid toxicity. This includes miosis or pinpoint pupils, respiratory depression, which again is manifested as slowed and absent breathing, and mental status depression, ranging anywhere from sleepiness to coma. Not all elements are always present, but if you see any of these things you need to think about opioid toxicity. And there are some other effects that can occur with opioids that aren't necessarily experienced by every overdose but are things that you should be aware of.
There's something called acute non-cardiogenic pulmonary edema. Sometimes patients will wake up after an opioid overdose, and typically within a few hours complain of shortness of breath, of cough with pink frothy sputum, and they'll have trouble breathing. Opioid overdose is a known cause of this, which is essentially a buildup of excess fluid in the gas exchanging parts of the lungs called the alveoli. It was originally thought to be due to naloxone, the reversal agent. But it was also found on autopsy of those who never received naloxone. So it's probably due to leaky membranes from the low oxygen that was experienced during the overdose. This is treated supportively, and may require non-invasive positive pressure ventilation, such as BiPAP or intubation, and mechanical ventilation with a ventilator.

Hearing loss is another effect that may be seen in the setting of acute opioid overdose. The reasons that this happened are unclear but some people theorized that there is a direct attack on the cells of the cochlea. Most commonly, this resolves on its own but sometimes cochlear implants are required.

Seizures can occur with any opioid and maybe to inherit drug toxicity versus low oxygen, leading to an irritable brain. There are few specific opioids however, that are classically associated with the side effect. Those opioids include tramadol, meperidine, or propoxyphene, or tapentadol.

There are also complications of excessive sedation and the condition of "found down." When this occurs, person will be in one position for a long period of time without moving or being able to adjust themselves. You can see it compartment syndrome, which is muscle breakdown from prolonged pressure leading to muscular swelling and threatening the integrity of the limb or the gluteal muscle, which has been compromised. Very often this co-occurs with renal failure as a result, because the kidneys get clogged with all the products of the damaged muscle. This can, you know, this can also be seen with anything that can make you sleepy or comatose to the point where you're not shifting positions. The complications of "found down" also include anything that would happen if you were incredibly sleepy or comatose, like balls or accidents, dehydration and so forth.

Some other things to consider are the effects of adulterants or co-formulants, in patients with acute overdose. In oral preparation of opioids, it's very common to have acetaminophen mixed in. For example, oxycodone acetaminophen or hydrocodone acetaminophen. In patients who either chronically abuse these or have an acute overdose are at risk for not only the opioid toxicity but acetaminophen toxicity as well. You can also have adulterants, which essentially are, you know, cheaper alternative things that are added into heroin, bulking up and make more profit. In the past, these have included things such as quinine, strychnine, clenbuterol, and so forth. Those have inherent toxicities on their own and can result in visual disturbances, cardiac ischemia, meaning, you know, heart attack, and/or cardiac arrhythmia. There's also the, you know, the chance that you may have emboli. So when you, you know,
When you do heroin for instance very often it's filtered through a cotton ball. Any little particles that are on that cotton ball or that don't get filtered can end up in the I.V. syringe and then can hence end up in your blood system and travel to your lungs, your heart, or anywhere else it wants to go.

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So this is a good graphic representation of the more common aspects of acute opioid toxicity. Items 1 to 3 are your classic opioid overdose toxidrome, which if you remember, is slowed or absent breathing, small pinpoint pupils, and stupor or coma. Some other findings like we just discussed can include liver toxicity from coingestions, like acetaminophen, or even lack of oxygen can cause that, too. You can see rhabdomyolysis, which is another name for muscle breakdown. Renal failure due to prolonged downtime, or compartment syndrome depicted in number eight on this image here, which is a swelling of the muscle in, you know, one of the muscle compartments. You can also see slowed or absent bowel sounds, or hypothermia. Item Number 10 is a reminder to look for skin patches, such as fentanyl, that could continuing- that could be continuing to administer opioids while you're trying to, you know, fix the patient.

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So next we move on to the chronic effects. You can see things like constipation, decreased libido or decrease sex drive, physical tolerance, meaning that the same dose of medication or drug isn't working the way it used to because you're tolerant to it, so you need increasing doses to get that same effect that you desire. Hyperalgesia, which is the phenomenon where you actually have increased sensitivity to pain when you're on opioids long term. Addiction, which we're all very familiar with. And complications of I.V. drug abuse itself- you know, not only do you have the infectious complications like HIV or hepatitis C, but you can also have skin changes, social repercussions and so forth.

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As you can see, injection drug use is a huge risk factor for contraction of hepatitis C. If you look at the bars here, of the risk, you know, the risk- the exposure risk and behavior, injection drug use was listed by 702 people. And by comparison, those men who have sex with men that was 27 people, sex or sexual contact was three people, multiple sex partners 150. There were a lot of missing data, so we don't know for a lot of those people. But from what we are seeing it's definitely, you know, not insignificant there. And like we said before, it's a risk factor for HIV transmission as well.

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So those were all the common effects for opioids in general. Now I'd like to take a closer look at the details of specific drugs.

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As mentioned earlier, fentanyl is a synthetic opioid, 100 times more potent than morphine. When this substance, or one of its derivatives is administered too rapidly, the muscles of the chest wall can become rigid and make it mechanically difficult to breathe. In severe cases, this can lead to respiratory failure. Another aspect of the fentanyl are their potency and potential for greater toxicity. The picture
here shows lethal doses of heroin, fentanyl, and carfentanyl, which is another derivative that is incredibly potent. You can see how something the size of a grain of salt can be lethal.

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This increased potency is reflected in the figure that we saw earlier. It's been responsible for a skyrocketing number of deaths in recent years. Again, represented by that dotted orange line.

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So again carfentanyl, which, you know, has been in the news recently, is a fentanyl analogue, meaning it looks like fentanyl which just a little, you know, few alterations and is orders of magnitude and stronger than fentanyl itself. Over the past two years or so, this has been confirmed in multiple overdose deaths. So it isn't widespread yet. Opiates at this potency have the potential to be used as a weapon of terror.

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We can conceivably see how this could be by looking at the Moscow theater hostage situation back in 2002. About 40 Chechen terrorists held 912 theater-goers hostage for over 40 hours. The Russian military pumped the gas into the theater to subdue the terrorists but it ended up killing 130 people in the process. The Russian military has denied that this was carfentanyl but testing that was performed after the incident does show evidence that that was likely the cause.

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And moving on, another opioid I'm sure you heard of is meperidine, brand-name of Demerol. This can increase the amount of the neurotransmitter, serotonin in your system, especially when you have other medications like antidepressants that can concurrently increase that same neurotransmitter. The result can be something called serotonin syndrome. Now, you know, mild cases of this people may feel jittery then you feel anxious, they may have a little tremor. Sometimes you can be sweaty. In severe cases though you can get extreme hyperthermia, rigid limbs, because your muscles are just contracting so much. You can have seizures and it can cause death. And again if you think back to the, you know, the seizure slide we had before, meperidine is one of the opioid medications that is more strongly associated with this side effect.

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So methadone is a long acting opioid that's used, not only for pain control but also for treatment of opioid addiction. What this does, you know, kind of when a chemical basis is it decreases the amount of potassium flowing out of the cells. So this can predispose to a prolonged QTc interval, which is a heart conduction interval. And that can lead to an arrhythmia, called polymorphic ventricular tachycardia or torsades de pointes, which can be deadly if not treated immediately. Another unique aspect of methadone is because it's so long acting, you can have delayed toxicity, meaning you know, your breathing can stop hours after the last dose ingested. So that is something important to keep in mind when evaluating these patients.
So the next opioid I'm going to talk about is loperamide, which you may not know is an opioid. This is an over-the-counter anti-diarrheal medication. So you can go to any pharmacy and buy it. But if you look at the structures here, it is incredibly similar to methadone and behaves like the opioid when taken in high doses. Due to Internet sites promoting this, there was a big spike in this practice around 2014 and 2015. People use it to treat symptoms of opioid withdrawal, or high-doser doses to get high. It's appealing because it's cheap and lethal.

Because it looks very much like methadone, you can have the same effect on the cardiac cells and the same side effects of heart arrhythmia, or polymorphic ventricular tachycardia.

Now codeine, again it's something I'm sure you've heard of—maybe even taken it for one reason or another. But this is unique in that the parent drug itself is not active. So it doesn't have any pain-fighting ability. It has to be metabolized by a liver enzyme called—called CYP2D6, into its active form or active metabolite which is morphine. So this is fine—you know, you have your normal opioid effects from this. But there are some people who are—they have a variant of that enzyme where they're rapid metabolizers. So they'll get the normal dose that's recommended of the codeine but then because they metabolize it so rapidly, they have a quick buildup of a lot of morphine all at once, and that can lead to a functional drug overdose. There is actually a black box warning placed in 2013 regarding the use of this medication in children for that reason.

Now this is—the next thing is called Krokodil. It contains desomorphine, which is an opioid. It's primarily seen in Eastern Europe. Not in the United States yet, but I wanted to mention it. It appears to be more injective than heroin, and it's easy and cheap to make. It has the same acute side effect profile as any other opioid, but the chronic affects are what sets it apart. It's synthesized using codeine and a variety of toxic constituents, such as gasoline, iodine, paint thinner, lighter fluid, or industrial cleaning oil. Those who inject it experience gangrene and tissue loss from the inside out, because those toxic constituents are just wreaking havoc on the tissues of the body. A nickname for this, is the zombie eating—sorry—zombie flesh eating drug. I haven't included pictures due to the graphic nature but you can easily look this up online if you wish to do so. Because the heroin supply is so readily available here in the U.S., I think that's a major reason that we haven't had to resort to this particular drug. When I say we, I mean, you know, patients who are—not patients but people who are heroin users. But if something happens with heroin in the future who knows they might be seeing this. What's sad about this is that patients who are users of this substance have a life span of about one to two years just because of all the complications with tissue loss and gangrene and infection that go along with it to use.

So onto the diagnosis of opioid toxicity and ways to test for it.
So the way we diagnose this is mainly a clinical diagnosis, meaning we examine the patient, look at the vital signs, listen to whatever history you have and make the diagnosis that way. Specific levels are possible. But typically you have to send them out to specialized labs and you don't get them back in any kind of timely manner. There are urine drug screens, which we'll talk about now.

Most commercially available urine drug screens are designed to detect morphine, via antibodies made against the drug. In this picture, the grey area as are parts of the structure that differ from morphine. Based on the structure, some opioids will cross react with these morphine antibodies. Others require very high concentrations to have significant cross reaction if the structure is very different.

This table shows what concentrations are needed to trigger a positive test result, which is equivalent to 300 nanograms per milliliter of morphine on urine drugs screens. Those three columns to the left are just different commercially available immunoassays, so they may vary just a little bit. Codeine, which is structurally very similar to morphine, only requires small amounts to be detected by these screening methods. On the other hand, buprenorphine and fentanyl, which look completely different, would need very high concentrations and will likely result false-negative urine drug screen.

Each opioid is metabolized a little differently, which is important to understand when interpreting urine drugs screens. If morphine is present for example, that could be due to morphine, heroin, or codeine. Hydromorphone could be due to hydrocodone, which is metabolized into hydromorphone, or the hydromorphone itself. Oxymorphone however, is only due to oxycodone. And 6-monoacetylmorphine, which you can see at the top, is only from metabolizing heroin, which is also called diacetylmorphine. The bottom line- with urine drug testing, is that you have to understand the limitations, and interpret results in the context of the reasons for which you are performing a test.

So next, I'd like to talk about treatment of opioid toxicity.

Naloxone is a reversal agent and is the mainstay of treatment for opioid toxicity. It's a competitive inhibitor of the opioid receptors and can be used in health care settings but recently has had a huge push towards outpatient use as well. Obviously, you should provide supportive measures as well, meaning, you know, assisting the breathing while you're getting everything ready. But this is the agent that will restore mental status and breathing.

As I said before, it's a competitive drug that attaches to the opioid receptor, stronger than most opioids. So it knocks off whatever opioid it was already there, and prevents any other opioids from acting. It lasts
about 30 to 60 minutes, so you may need to re-dose, depending on the duration of action of the opioid that's there.

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Dosing recommendations very slightly between sources, but this one from the New England Journal of Medicine is the one I like to use for inpatient or emergency department settings. The goal of naloxone is not to wake the patient up completely, but instead to have them breathe at an acceptable rate and be awake enough to protect the airway. You don't want to overshoot because you can precipitate acute withdrawal, which can lead to pain, vomiting, and agitation. Often times patients will elope from the emergency department for a variety of reasons, which can be dangerous if a long acting opiate is involved, such as methadone, because Naloxone will wear off and they will revert to whatever state it presented initially. Now, you should be supporting their aspirations with supplemental oxygen in a bag-valve mask, which is used to push air into the lungs throughout the period of toxicity. If you can't do this and they're already not breathing or barely breathing, that is a situation where I would opt for the larger dose of this reversely agent. Otherwise you should start low. At 0.04 milligrams intravenously. Wait two to three minutes while continuing to support their respirations, then give 0.5 milligrams. Wait another two to three minutes, then administer 2 milligrams, 4 milligrams, 10 milligrams, or 15 milligrams. With the more potent fentanyls out there, larger doses of naloxone may be required. I've heard stories of patients requiring upwards of 30 milligrams for a reversal. The moral of the story is not to give every patient 15 or 30 milligrams, but you should not stop if you give two milligrams, and everything else points to this being an opiate overdose, and reversal is needed. Just consider it. The initial pediatric dose is also listed at the top and that will be 0.1 milligrams per kilogram of body weight to start.

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So since 2006, non-medical professionals have been able to administer naloxone in the setting of opioid overdose. It's available in a few different forms. And the top picture there, you can see the intra-nasal form, where an atomizer is used to convert the liquid into a spray for the nostrils. The middle picture is an injectable form that can be given intra-muscularly in the thigh or in the arm, and there's also a talking auto-injector as well. Almost like an EpiPen. Sorry about the brand name but there is no generic for this yet. I feel like most people are pushing for the intranasal- intranasal version, because you avoid the chance of needlestick, and the lay public- it's probably more likely to make the decision to spray stuff up the nose rather than inject a needle into the thigh or arm. In New York State, you can obtain naloxone via prescription from a health care provider. You can go to a pharmacy, and many of these pharmacies have standing orders, meaning that they have the order to give them naloxone, but you as a patient or person don't need to bring in a prescription. You can also go to one of over 450 opioid overdose prevention programs. And if you visit that website, you can see where those are located. New York State has also tried to help the naloxone effort by coming up with something called NCAP, which is the Naloxone Co-pay Assistance Program. And what that is, is if you have a health insurance with a prescription drug coverage plan, this program will provide up to 40 dollars in copay assistance for anyone looking to obtain naloxone.
So in April 2014, law enforcement in New York State were trained to use naloxone. And since then, over 10,000 officers have been trained. This is really important and a great step because as you can see, police were on scene first, 91 percent of the times that there is a call for opioid overdose. As of April of this year, over 3,000 doses of naloxone were administered by law enforcement officers, and 88 percent of those patients lived.

So next I just want to show you a video of how to administer naloxone.

- [Narrator] So this is one full dose of Narcan. These are all the three pieces that come in each dose that we give out at down the AHOPE needle exchange program. And the way that you put this together is super simple. I'm going to take the applicator and I'm going to take these two yellow pieces off that you see here. So the first one, and then two. And you'll see that there is a tapered end here in an open end with a needle. And that will allow this applicator to access the medication. The second thing I'm going to do is I'm going to take this vial of medication, and I'm going to put this on the cap- it'll be either red or purple. And I just grab it underneath- I put my- my fingernail underneath, pop it straight off, and in the inside you can see a rubber grommet. What I'm going to do is I'm going to put the two open ends together like this, really gently, and twist until I start to feel the resistance. Then I'm going to take the atomizer and this turns the liquid into a spray, and allows a liquid to go up through the nose and enter through mucosal membranes, and then enter and pop the opiates off of the receptors in the brain. So I'm going to take this atomizer, twist it on the top like this. Now, this is one full dose- it's ready to go. So what I'm going to do is I'm going to go ahead and administer it, and a spray half up one nostril, and then half up the other. The whole thing how-

- [Alicia] So this is just a reminder that in New York State there is a 911 good Samaritan law enacted in 2011, which protects you from prosecution for sharing drugs or having paraphernalia if you call 911, assuming you don't have a warrant out for your arrest or other extenuating circumstances.

So next I'd like to talk to you about treatment options for opioid addiction.

So there are many Americans suffering from opioid addiction. This isn't always the case. But often there are concurrent social issues and coexistent psychiatric illness complicating drug dependency. Therefore, a successful treatment regimen is one that involves multiple approaches.

From the psychiatric side of things, behavioral therapy and psychological support are going to be incredibly helpful. Social support is also needed, and may include groups like Narcotics Anonymous,
familial support and so forth. There are also medication assisted treatments available to help with opioid addiction, which include naltrexone, methadone, buprenorphine, and we'll talk about it but potentially something called kratom in the future.

So naltrexone is a competitive opioid receptor antagonist. That means that it block- it binds to the opioid receptor and doesn't allow other- any- sorry- doesn't allow any opioids to come and activate it, as long as it's there. This can be used once opioid detox has occurred and is helpful for maintaining abstinence. This is appealing for those who do not want to take opioids such as methadone or buprenorphine, such as impaired health care providers. It can be taken orally or injected intramuscularly once a month. The major problem with this option is a lack of compliance and subsequent relapse. So the best population to use this are highly motivated individuals. It can also be used as an adjunct for alcohol dependence.

The next two options are methadone and buprenorphine. These are both effective at reducing opioid craving, treating pain, and preventing relapse. Methadone has been around since 1947 and dispensed in clinics since 1974. It's a synthetic new opioid receptor agonist, meaning it produces an effect at the opioid receptor. What this does is that it replaces whatever opioids were being used or abused with a legal, oral, and long acting opioid. Some people are hesitant to use opioid replacement therapy given the stigma attached to opioid use, and there are even national organizations like AA who condemn their use. However methadone has been associated with increased survival, improved birth outcomes, decreased illicit drug use, less transmission of blood borne infectious diseases, and less criminal acts. Another advantage of this medication is that it's relatively cheap. The disadvantages- one of which we talked about earlier, which is the cardiac toxicity and the potential to cause that deadly arrhythmia. Because of this, patients need to get each EKG to check on that interval that we talked about. Another disadvantage is that patients who are on methadone at least in the beginning have to go to the clinic every single day to get their medication dose. And there isn't a major take home option, such as a monthly prescription that you would get from buprenorphine. Another disadvantage is that there's no ceiling effect. And when we say ceiling effect, we mean that, you know, a ceiling effect is when increasing doses of a no good medication, you know, kind of depress respirations just to a certain extent, if any, but don't go any further with higher doses. With methadone, that's not the case when you have the potential to stop breathing if you take or are given too much.

Now buprenorphine on the other hand, has a ceiling effect, meaning that, you know, in patients with- in patients taking- in patients taking this, as long as there are other concurrent sedating medications and as long as they are adults, then typically this doesn't affect their respiratory rate to any significant amount. So in theory it's safer. Buprenorphine is a partial mu opioid receptor agonist, meaning that it binds to that receptor and produces only part of an effect, and it's enough to kind of help with cravings and prevent relapse. This has been FDA approved since 2002 and it can be given under sublingually or under the tongue, intravenously, or even in skin patches. It's often co-formulated with naloxone, which
has no effect if taken underneath the tongue, but it's a way to deter people from injecting the drug intravenously, because it prevents the high, and may even cause withdrawal. So other advantages besides having a ceiling effect of buprenorphine are that it can be prescribed in the office setting rather than in clinics, and you can, you know, you don't need daily visits in order to get your dosing; you can have monthly visits with this. Disadvantages are that there are limited number of prescribers that can administer this medication. In order for a physician to be able to prescribe this, they have to go through special training and get an x waiver that allows them to do this. And even when they have that, they can only dispense this medication to- or prescribe this medication to a limited number of people. So again, that doesn't make, you know, it doesn't give the best access to this medication that we would like, because of those limitations. This can be more expensive than methadone, which can be a disadvantage to some patients and because it partially activates that receptor but also, you know, partially- doesn't, it can induce withdrawal.

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This is another interesting part that I wanted to include for you. There is a plant called Mitragyna speciosa, and from that we derived a substance called kratom. It's from Southeast Asia and has been popular for long periods of time there. But it has only recently made its way to the United States, not only as a recreational drug, analgesic, anxiolytic, but for some they report it as a way to detox from opioids without the bad withdrawal symptoms.

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Now kratom contains over 40 different alkaloids in the plant. The most important of which are mitragynine and 7-hydroxymitragynine. Now, mitragynine is three times more potent than morphine, and 7-hydroxymitragynine which is only found as, you know, it's only 2 percent of the plant's alkaloid. But that is 17 times more potent than morphine. Now this is really interesting because for some reason that we don't entirely know why, there is no respiratory depression associated with this substance. You also see dose-dependent effects, meaning that at low doses it acts like a stimulant, so almost like a strong coffee or a weak cocaine. But at larger doses, you seem more of an opioid, you know, toxidrome type of picture, but again, without the respiratory depression. So kratom is currently legal to possess and consume in the United States. There, you know, in December of 2016 the DEA said that they were going to make the schedule 1, but there is a public outcry and they had a hearing period where people could write in and, kind of give their side of things, and currently we were waiting on a decision, whether or not this will remain legal, whether it will be schedule one, which is as illegal as heroin or something in between. Because this substance activates the opioid receptors and helps withdrawal but doesn't have the negative side effect of respiratory depression, it may be a promising treatment for opiate addiction in the future. But again, if that becomes scheduled, you know, the same way that heroin is, then that's going to be really difficult to do. So just something in case you hear it and want to know what it is.

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So next, I want to talk about opioid withdrawal. So when you use opioids long term, your body gets used to the receptors being occupied. When you stop using or given a reversal agent, all of the sudden these
receptors are empty. You essentially develop signs and symptoms which are commonly the opposite of opioid intoxication. Instead of small pupils, you have large ones. Instead of somnolence, you’re agitated. Instead of constipation, you have diarrhea. There are also a few other hallmark symptoms, like yawning, rhinorrhea or runny nose, nausea and vomiting, and goosebumps. These are unpleasant but typically not life threatening. Treatments can include opioid replacement therapy or clonidine, which is helpful for flanking the sympathetic output that’s causing some of the unpleasant effects being experienced.

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So newborn babies can also experience withdrawal in something called neonatal abstinence syndrome. Despite opioid use throughout history, the first report of neonatal withdrawal symptoms upon birth was in 1875, and it was named congenital morphinism at that time. Most infants died, until a report was published about the successful treatment of this condition, morphine. Since then, recognition and awareness has increased. All opioids, including prescription medications, methadone, buprenorphine, or illicit opioids have been associated with this entity. Usually, it occurs within one to three days following birth, although symptom onset may be delayed for babies who are born to mothers who were taking the longer-acting opioids. These longer acting opioids can also have a longer duration of symptoms. In some cases, over a month.

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So a variety of clinical effects can be seen with neonatal abstinence syndrome. It’s not mentioned in this figure, but seizures can also be seen. So starting at the top, a corticotrophin release causes stress and increased eating. Going clockwise, we can see that a decrease in the neurotransmitter, dopamine, leads to irritability and anxiety. Increased acetylcholine can caused nausea, vomiting, and diarrhea, sneezing, sweating, and yawning. Babies will feel increased pain even with normal stimuli. An increase in noradrenaline, which is something we call, you know, increased sympathetic output, can cause hypertension, tremor, increased temperature, and a high heart rate. And lastly, lack of serotonin impairs sleep, which is not something you want in a newborn.

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So the way we treat neonatal abstinence syndrome is by a few different modalities, one of which is calming measures. This can include swaddling the baby, rocking the baby, and placing the baby in a low stimulation environment. We also recommend that the babies, you know, have- promote their sleep. So, you know, dim rooms, try not to wake them- those are going to be important. Morphine decreases the incidence of seizures. It improves feeding, eliminates diarrhea, decreases agitation, and can control severe symptoms of neonatal abstinence syndrome. Methadone and buprenorphine are less well studied than morphine, but may be ideal choices if the mother was taking these during the pregnancy. Phenobarbital is an option but usually this is used as adjunct therapy for polypharmacy abstinence syndrome, meaning, you know, the mother was using multiple substances, not just opioids. And lastly, clonidine may also have a role with this, because it- because of that increased sympathetic response that we talked about, it can help to blunt that and kind of, take those symptoms away.
So in summary, I just have a couple, you know, a couple of bullet points that I want to go through with you, just to give you what I think are the highlights of this talk and what I would want you to take away from this. So the first is that an opiate is naturally derived, while an opioid—any substance that binds to the opioid receptor to produce an effect. The classic opioid toxidrome, which is the hallmark of opioid toxicity, includes pinpoint pupils, respiratory depression, and mental status depression. Increased prescribing practices have fueled the opioid epidemic. And this has been further compounded by the ease of obtaining drugs off the Internet and increasing the availability of high potency opioids. The rates of death from drug overdose, including opioid overdose have continued to rise. Fentanyl and other high potency derivatives are causing a dramatic increase in drug overdose deaths. Naloxone is the mainstay of opioid treatment, and patients should be educated on how to obtain and administer this lifesaving medication. There are multiple options for treatment of opiate addiction that the most commonly a multifaceted approach should be utilized. And lastly, urine drug screens are imperfect. Know their limitations, and understand how to interpret the results that you obtain. Thank you very much. If you have any questions, feel free to email me at the address listed and I'd be happy to answer.

- [Tia] Thank you Dr. Lydecker for that excellent overview on opioids. You've been listening to a learning module that has been funded through a grant from the New York's AIDS Institute.

[Video end]