Pharmacology & Toxicology - Nelson

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This presentation is entitled Pharmacology and Toxicology: Principles, Applications and limitations. I will now pass it over to Dr. Lewis Nelson to begin our presentation.

00:10

Good day, everybody. I'm Lewis Nelson. And it's really a pleasure to be here to talk about my favorite topic. And, and one I know that is, you know, both exciting and, and sort of daunting to many people that are that are watching this. I am the chair of Emergency Medicine at Rutgers New Jersey Medical School. I'm also a medical toxicologist and you know, medical toxicology is the study of poisons and overdose and many of us in med toxic sort of segued a lot of our career through the substance use pathway into addiction medicine, and I've gotten my boards and have a pretty thriving practice in addiction medicine too. So I really feel that some of the material I'm going to cover, while it may seem fairly basic and fundamental, it is it is exactly that- it's it's understanding the fundamentals of Pharmacology and Toxicology and how they apply to the patients that you will be taking care of it. Like anything else, kind of understanding the basics really helps you think outside the box, and just provides a context for really understanding what you're doing, why you're doing it. So I have no financial disclosures.

01:21

To, to make and, and the learning objectives, as you'll see here, and I'll let you read through them really are going to are going to represent how the talk is broken down really understanding some of the pharmacological principles, particularly pharm- pharmacokinetics and pharmacodynamics. And, and how using both opioids and stimulants, and a few other alcohols as examples, how they're relevant to your daily practice, and how they really will impact the care that you provide.

01:50

At the end we'll spend little bit time talking about drug screening and drug testing. I think that's a big part of what we do. It's it's a huge topic, and I think we'll scratch the surface. And during the, during the talk, if you have any, any questions that you'd like to raise, please just put them in the chat. And I'll try to address them as we go along.

02:09

So as I said, addiction medicine is pharmacology and pharmacology is such an important part of, of everything that we do in medicine, I mean, there's essentially no specialty medicine that doesn't use some sort of medication. We have the added benefit really having to deal with the other side of pharmacology, which is non- the non therapeutic side as well, which is the use of drugs for the for the feelings they elicit and things like that. But in order to get a response. And I think this is obviously something that everybody understands- drugs have to get into the brain, it's the brain where everything occurs, and we have a built-in barrier to drugs getting in. And that's the blood brain barrier. And so many of the things that we do, and so much of the reasons that we choose the drugs to use that we do is because they're able to get through that blood brain barrier in effective- in an effective way. And and we'll go through a lot of these principles as we go through this.

03:00

But, but a fundamental understanding is, the more rapidly a drug gets into the brain, the more likely it is to produce reward and euphoria and, and reinforcement. Part of that is related to dose and dose rate. And dose is how much you give and dose rate is how quickly you give that dose. So a milligram over a minute, versus milligram over an hour,

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The route of administration is very important, we're gonna talk a lot about the difference between oral and intravenous and, and intranasal. And then other pharmacological characteristics, primarily, the one that we really think about is lipophilicity. Because if you think about lipid solubility, the blood brain barrier basically is just a lipid. And in order to get through that lipid, you have to be able to be to be soluble. And if you're not soluble in it, it will be excluded, that drug will be excluded to some extent from getting into the brain.

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And we're going to speak a lot about these two terms. And I just want to remind everybody what they mean, because some of you probably haven't used them regularly since medical school. But pharmacokinetics is the movement of drugs around the body. And pharmacodynamics is the effects that those drug have on the body. And you can see that I've sort of broken this down into a few different buckets, with most of them falling neatly into one or the other bucket- drug interactions having both pharmacokinetic and pharmacodynamic. aspects. And when we talk about drug interactions, we'll mention that as well. And again, we're going to talk about all these terms. Just, just plant them in your brain so that we go forward, you'll remember them.

04:28

Dose response- very kind of simple concept. The more drug you give, the more response you're going to get. And drawn out diagrammatically. You'll see on the left and the right, these are representation of the same of the same information. On the left hand side we still have a population response. You

of the same of the same information. On the left hand side we still have a population response. You can see that some, at some, some people in population are exquisitely sensitive to a drug and they have a response at a very low dose and some need a much higher doses to have the same response.

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Drawn out in a more curvilinear fashion on the right, which is something we typically are more likely to see, is a more conventional dose response. So, remember, dose is what it is. It's milligrams, micrograms per whatever. And response could be the response to whatever aspect of the clinical effect that you're looking for. I've listed a few there. Often we look at things like, like euphoria, right? How much, which drugs take to get high. It could be death, in which case, we don't think about this as saying LD50, right, the dose it takes to kill 50% of the people,

05:26

Those responses, those responses come in a bunch of different flavors, so to speak. And you can see I drew the classic ones but but these are U shaped, or sometimes called J shaped dose-response curves, where where you kind of see that, on the left hand side, that a substance may not have much of an effect, if you don't have it, but a little bit of it, is actually beneficial. And as you get an increasing amount of that drug, it actually becomes toxic.

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And, and just as an example of that would be something like ethanol, where we think at least it's a... the French paradox that red wine, red wine may actually be healthy... for vitamins you see it too- probably most people would die without vitamins. But certainly vitamins are healthy, and you need them. or healthful, you need them. But as the dose goes up, clearly, there are some problems.

06:13

And the other side, there are things that you literally can't live without, without dying, so you need some of it. And those same substances at higher doses can be potentially lethal. Examples of that would be things like oxygen and water. We don't usually think about dose response curves for these things, because they're not necessarily medicines, but they're part of, of our body. And certainly they have pharmacological properties to them as well.

06:35

I like to think about potency, because potency is a big part, it's a big word in our in our vocabulary in our vernacular, and I think it's often misused a little bit. Here's just a quick quiz. Just think about it in your mind, if you were to rank order the potency of these different agents, how would you do that? Right? In other words, which would be the most potent? Or how would they relate to one another? Right, and I'll just give you a second think about that. And I'll give you the answer.

06:59

The LD50. In other words, how much of it take- how much of a drug does it take to kill you is actually quite disparate, right? Ethanol, which many people think is fairly potent is actually quite non-potent. It takes grams of alcohol ethanol to to get drunk or certainly to die. Whereas morphine and nicotine, which we don't really think of them as being particularly, or certainly we don't think nicotine has been particularly lethal, the amount of drug it takes to kill you with nicotine is about the same, at least potentially, as it takes to kill you from morphine. And botulinum, which is probably the most potent substance that we ever really will face is exceptionally potent; it takes exceptionally those picogram doses, really to have a clinical effect. So recognize that potency is a funny term. And you got to be careful not to confuse, confuse potency with clinical effect, which a lot of people do. And we'll we'll talk about some examples of that as we go through then here.

07:50

Here's a quick one. So which which of these two forms of cannabis is more potent or has more potent THC: the way that you might have smoked in college versus the way that's used more conventionally now that's sold in dispensaries?

08:05

Clearly the amount of THC is different from the 4% of the 20%. But it's a bit of a trick question because THC itself has the same potency. THC is THC. Some would say that the weed today is more potent than the weed from the 1980s. But that may not really be the right terminology to use, although conceptually it's easy to say. And we sometimes say things knowing that we're not using the right terminology. Really, there's different concentrations of different of the different cannabis forms, right, but the potency of THC is exactly the same, it hasn't changed. You can argue that it takes less 2020 weed to get high because the concentration of THC is higher. But just be careful with the words that's all... you know, I tend to be fairly word specific and, and I think many of you are as well.

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But when it all comes down to it potency isn't even relevant. Because you can see that all of these medications could potentially kill you if you take enough of it. So it's very easy to overcome potency, just by taking more of the drug. We think of carfentanil I'll give you some examples later of carfentanil, but you know carfentanil's perfectly fine drug if you take a low enough dose, right, obviously take too much it's going to kill- if you take too much tramadol it's going to kill you also, and we consider that to be exceptionally impotant or nonpotant. So, again, terminology matters.

09:28

The whole basis of pharmacology is based on this very, I think simple statement which I can further simplify to say "dose makes the poison." Right? A foreword, some sort of a title or subtitle for all medical toxicology. Really, the more you take of a substance, the more likely it is to cause a problem. We think of oxygen, water is something that you can't get sick from, but you can get sick from both of them. Everything is poisonous. It just depends on the dose. That's Paracelsus from, I don't know, several 100 years ago.

10:02

So here's the example. All right, we think of heroin and fentanyl and carfentanil, as opioids. They have the same pharmacological effect and recognize that that at the proper dose, they're all equivalently safe and we use fentanyl all the time and people die of fentanyl all the time, but it's perfectly safe drug when used with the right dose. carfentanil is used... You know, it's an animal tranquilizer called wildnil we don't use it in humans, but it's perfectly fine in animals and animals are basically just people. So there's no reason to think you couldn't use it in people if you use the right dose.

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Of course, you can lower the dose of heroin and add carfentanil to it, to lower the dose of fentanyl and add carfentanil to it and you could still give a safe dose. If you don't lower the dose of heroin but you still give a little carfentanil, it becomes dangerous. And these are the people that overdose but don't necessarily die. They might have respiratory depression. They might need naloxone. And there are dangerous doses. Or if you get a little too much of the carfentanil. Of course, if you overdo any of them, and that balance isn't right, you die, or they die. And this is exactly why it's important to understand the concept of potency. Because you can definitely give very potent doses, say very potent medications or drugs very safely.

11:16

Let's talk about absorption. Everybody recognized there are multiple different routes of absorption. Most of the drugs we talk about medication certainly were given orally, and they suffer certain effects like first-pass metabolis. We're going to talk a bit more about some routes of administration eliminate or bypass first-pass metabolism, which means that it goes up through the liver and gets metabolized away. The only route that probably uniquely bypasses the blood brain barrier is intrathecal. But there are no drugs that we give, that we would be talking about in our world, at least, that we think about giving intrathecally. Of course, some drugs are given that way, but not not typically by by people practicing emergency medicine, or addiction medicine or medical toxicology. You can read a little bit about the rest of these.

12:04

But I want to point out this last one because I think it's pretty fascinating, which is something we don't really appreciate. The fact is when we give naloxone intranasally, it works a lot faster than you think it should. Because in order to work by being absorbed through the rest of the epithelium and circulates through the blood, and then getting into the brain, it should take a while. But it tends to work within one or two minutes, which is a lot more quickly than you expect it to work. And that's probably because there is nose to brain passage right up to the cribriform plate along the olfactory nerves right up into the brain. And it has and we're recognizing we pharma- pharmacologists are recognizing more that there may be some therapeutic value to drugs administered intranasally. So just something to think about.

12:50

Bioavailability is important. This is the amount of drug that gets into the systemic circulation after administration. And bioavailability, which is usually defined in formulas as F depends upon a few things: the route of administration. So when you give something IV, it's pretty much in your body, it doesn't rely on any absorption. So we consider that to be one or 100%.

13:12

Site specific membrane permeability: you know, we talk about how permeable the the oral mucosa is the- the nasal mucosa the skin if something's permeable or not.

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Drug transporter activity: we'll talk a little bit later about p-glycoprotein. And how that affects how easily a drug gets in or out of a ver- of a certain organ. And then first-pass metabolism, which we've already mentioned that we'll talk a little bit about later.

13:36

But just to give you an example. You know, buprenorphine we know, if you eat it doesn't work very well, but sublingually it's got a much higher bioavailability and we can largely rely on that route in order to be absorbed. Naloxone same, I mean, we think about it orally, it's just eliminated completely by the liver, which is one of the reasons we added to the to the buprenorphine-naloxone combination formulation because we know that the bupe will be absorbed sublingually, the naloxone really has much poorer oral and sublingual bioavailability.

14:13

And then if you look at morphine and oxycodone, you'll see both of them are orally administered medications, but morphine's got fairly poor bioavailability whereas oxy which is typically preferred, for pain, by pain management, for for pain management, has better bioavailability. There are issues, of course with with oxycodone's bioavailability because part of the the issues that we deal with with oxycodone later on will be its lipophilicity and its ability to enter the brain and its and its rewarding potential. But at least from a bioavailability perspective, you can see that you can you can absorb more of a given dose. So if you take the same dose, you would absorb more oxycodone, we typically give more morphine to overcome that. So a typical morphine oral dose might be 15 milligrams, whereas an oxycodone dose might be five milligrams

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But what's really important to recognize is that bioavailability is one factor and the rate of absorption is one factor, but so is the total absorption of that medication. And we we think of the total absorption of a medication as the area under the curve. So if you were to measure and we'll go over more examples, as we go through this, the amount of space under IV, IM and sub-cu, for a given dose of

drug, they would all be the same, you can see that the actual kinetic characteristics are different. So the peak and the and the rate of elimination differ, but the amount of drug under each of those are the same. Under PO if you want to add that would be probably a little bit lower, because people usually has some loss either through metabolism in the GI tract or metabolism in the liver. So the total bioavailability the area under the curve, the total amount of drug absorbed is usually a little bit lower with PO but seems sub-cu, IM and IV will bypass hepatic metabolism. The amount that you give, will be absorbed completely just at different at different rates at different kinetic characteristics.

16:08

When you think about a drug like oxycontin, they were able to take advantage of some of these characteristics. So. so remember that the pill was made to sort of simulate a slow absorption environment by by elim- by by having a large amount of drug available in a pill but released over a much longer period of time, we were able to sort of change the oral absorption characteristic of that drug. Unfortunately, as, as even the advertising told you almost with a wink and a nod that if you break those pills, you will eliminate the controls release, or sustained release mechanism and allow rapid absorption of all of that medication. So just looked at a little bit more formulaic. If you think about each of these oxy IRs containing 10 milligrams, versus the oxy ER containing 30 milligrams, if you were to add up the amount of drug absorbed in each of these different 10 milligram doses with the amount absorbed under the 30 milligram, ER, extended release formulation, they would be equivalent, but you can see that their kinetic characteristics differ. One is higher peak, and then it rapidly falls off higher peak and rapidly pulls off versus slow and smooth, continuous absorption. Now if you were to crush it, you would absorb all of that 30 milligram oxy ER at once and it would sort of mimic the oxy IR kinetics curve, but with a much higher peak, right, because you'd be absorbing three times the amount of drug. So but again, if you were to add up, the amount of drug absorbed, whether it was released properly or released in a crushed formulation, they would both be the same, right? Because it's the same amount of drug being put into your GI tract.

18:04

That is really what happened with with OC, right that was oxycontin originally. It was reformulated in 2010 to have a tamper resistance or an abuse deterrent formulation, which people were able to figure out how to get around and convert OP essentially back into crushable or functionally crushed OC and able to get the medication out of it. But this is how street pharmacologists work and they spend a lot of time and they talk on chat rooms like Blue Light on exactly how to do these sorts of things. But you can see why this drug became so dangerous. It took- it's really because it's really the peak level that we're concerned about when it comes to overdose. Of course, it's the- it's the lingering level that we talk about when we talk about some of the other pharmacological properties, maybe addiction, maybe hyperalgesia. But certainly, from an overdose perspective, it's the peak that's most concerning

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A biotransformation involves the conversion of medications generally from lipophilic forms which are not water soluble, and eliminate- eliminatable by the by the kidneys, to something that is more amenable to renal elimination. That's generally what we think about with phase one. And phase two reactions. And not all drugs undergo both phases, some undergo only phase one, some actually

undergo phase two without phase one. So it depends a little bit on the drug and the needs. And then there are other systems and we talk a little bit of we'll talk a little bit more later about alcohol. But most alcohol is eliminated through alcohol dehydrogenase where we convert alcohol, which is fairly water soluble, to something that is even more so through the use of ADH.

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But there are other mechanisms to eliminate alcohol as well. Typically ADH performs the majority of our alcohol elimination, but with chronic and heavy use, we induce two to one, one of the cytochromes and we're able to eliminate more through that means

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Sometimes biotransformation can actually activate things. Andwhen we think about or activate medication we think about codeine, which itself is inactive and not a very functional opioid and as long as you have 2D6, which most people do- about 7% of the population does not, codeine becomes morphine and then metabolism through demethylation makes that codeine an active- an active medication active drug. So codeine really is a pro-drug. And lisdexamfetamine is the same, it gets metabolized to amphetamine through biotransformation.

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Just as a fun fact that I think many people know this already. But, but heroin itself, like codeine, does not bind to the opiate receptor and have any effect. Codeine has to be metabolized to more- I'm sorry, heroin has to be metabolized to morphine in order to be functional. Right? It turns out that, just like with codeine, heroin has more- is more lipophilic. And it's much more rapidly able to enter the brain, it's able to cross the CSF, and we talked about lipophilicity as being a key parameter on how quickly a drug can get into the brain.

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So functionally, heroin is a carrier molecule for morphine, to bring it into the brain. It turns out in the brain, we have an exceptionally functional system called cholinesterase, that's able to metabolize those acetylcholine molecules off of the heroin. Right? Remember, that's all that heroin is- is diacetylmorphine. So if you take those two acetyl groups off of the more- off of the heroin, it becomes morphine. It would almost be like injecting morphine directly into the brain- intrathecal administration, so heroin is almost equivalent to giving morphine intrathecally. Right, and that's why heroin is so much more enjoyable than morphine would be. And that's why morphine isn't sold on the street and heroin is because nobody would really enjoy using morphine, there'd be no- there would be no sale value to it.

21:46

This is a busy slide, I'm not going to go through it in detail, but something you could look at if you're interested. I just want to point out biotransformation involves things like polymorphisms. And we think about 2D6, for example, as a drug with a lot of polymorphisms. And, and how it affects our

think about 2D6, for example, as a drug with a lot of polymorphisms. And, and how it affects our ability to use medications. Certain or or, or to both to negatively and positively impact medication use. So you know, 2D6, for example, is important in the metabolism of drugs like diacetylmorphine, right, and we could see how certain people might have more or less of an effect from diacetylmorphine based on their 2D6 polymorphism.

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But, but polymorphisms in and of themselves aren't simply the issue because sometimes we can, we can eject, we can sort of make a polymorphism through drug interaction. And I think about a drug like 3A4 which is a major cause of some of our, quote, unquote, polymorphic effects through the use of inhibitors. And we think about methadone as an example. Because we remember back when, when, during the HIV epidemic, when we- when people were choosing to take their HIV meds, which induced 3A4 and increased the metabolism of methadone, or they were just stop taking their me- HIV meds because they would wind up suffering from opioid withdrawal from the rapid metabolism of methadone.

23:09

Now, we can also use this to our benefit. A drug like paxlovid, which contains ritonavir is is a 3A4 inhibitor, and that that limits the metabolism of the other components of paxlovid so that it doesn't get metabolized away too quickly. So there are a lot of beneficial effects of of understanding polymorphisms or even induced by morphisms, which again, we think about as drug interactions to some extent, but they're intentional, they're they're, they're desirable.

23:38

Distribution: we talked about first pass. Just remind you, that drug gets into the GI tract, and almost everything that you absorb from the GI tract, except, you know, through the very upper reaches and the very lower parts, the tract- go through the portal vein, and into the liver where, you know, metabolism could be non-existent to complete as that medication passes through the GI tract. We can bypass that, as we do when we use drugs intranasally, or transdermally. Or sublingually, for example, as you see with some of these medications. And we take full advantage of the fact that we can bypass metabolism. But there are some other interesting implications of this.

24:19

So if you look at the graph, on the left, you'll see typically, you know, after a typical dose of cocaine, whether it's given IV, IN, or smoked, the plasma levels generated based on the same relative dose of medication vary fairly dramatically. Right, so you'll see that the smoked- a smoked dose of crack gives you a level of about half of what the same dose of of the drug would be when you give it intravenously.

24:48

On the right hand graphic though, you'll see the clinical effects of those doses and there's a real

disconnect, at least you can see with the smoked version. There's a fairly direct correlation between the cocaine dose and the cocaine effect when it's given intravenously or intranasally, but because the smoked is much more lipid soluble, and I'm going to go into this a bit later, you can see that the clinical effects of this- of smoked cocaine, meaning meaning cocaine based on cocaine salt. The difference in the clinical effects that you get after smoking crack than after injecting or snorting cocaine are fairly dramatic. And I think this is a slide that nicely conceptualizes that

25:35

We think a little bit about steady state. Remember that it doesn't matter what drug you take, it takes about five or maybe six half lives to get to steady state, depending on how much you want to get up to 100%. It's all based, essentially, on the half life. Now it doesn't matter how long the half life is, it's still five half lives. So 1 minute half life or 2 day half life... it still takes five of those half lives.

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And that explains a little bit the difficulty in inducing or you initiating methadone in our patients, because A- the half life is long, so it takes many days to get to steady state and B- the half life is variable. And so some people have a fairly short elimination time, and some people have a long elimination time. So if you go up too quickly in people with a long elimination half- half time, or half life, they stack doses and they wind up becoming sedate and potentially even suffering, you know, respiratory compromise and, and dying. So that's the most dangerous period, of course, is that initial few days of getting started on methadone.

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Things might have changed a little bit with fentanyl. And methadone may be both more desirable as a drug to use, you might need higher dose, it might almost be quote unquote "safer to use." But still, the concepts are the same. That methadone is a tricky drug to get people started on.

26:47

When a drug is given, you know, almost all medications cross passively through our membranes, and there's lots of different layers it has to go through to get into the organele. Here we're talking about the brain, for example, it has to get through almost all medication and all drugs that we use is passively able to passively enter into the organ of interest. There's very few active uptake mechanisms for the medications that we use. So this diffusion of filtration with bulk flow gets through channels or gets through the membrane itself is really important. That's why lipophilicity becomes so important. Things that are able to make their way through membranes, because of their lipid concentration, or their lipid characteristics really important. Remember, if you're too lipid soluble, it gets stuck in the membrane. If you're not lipid soluble enough in your chart, for example, you can't even enter the membrane. So you need to have that right balance between lipid and water solubility in order to get into the brain, which is why not every drug is useful. As a as a mechanism.

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To get to get high, for example, every psychoactive drug does not get you high because you can't get into the brain and we use this pharmacologically, or in pharmaceuticals to actually change the characteristics of some drugs. That's why we have some drugs that are peripherally restricted opioids, for example, or opioid antagonists, for example. So they're good at getting to the GI tract and and inhibiting the effect of an opioid on those receptors, but they don't get into the brain and precipitate withdrawal. And we think about things like methylnaltrexone, as an example of something you might think of is as peripherally restricted opioid antagonist.

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There are active transport mechanisms out for the most part, not so much in at least when it comes to the medications we use as a some drugs can be taken up by the organic transport- or organic anion transporters. But clearly, the p-glycoprotein is this very nonspecific mechanism that pulls drugs out of the brain and puts it back into the blood. And we know about these, and so do street pharmacologists and, and an example here would be using P glycoprotein inhibitors to prolong the effects of loperamide. And we think of drugs like loperamide as something that are normally not very psychoactive, they're not- they're able to get into the brain. So they're not peripherally restricted per se. But the but the P glycoprotein mechanism is so effective at pumping it out of the brain that functionally you can get high. Even with fairly large doses, you can escalate to dose- loperamide, it's a fairly cheap medication to buy.

29:17

If you give people like a protein inhibitor like cemetidine, it actually prevents the expulsion of, of loperamide from the brain. So it becomes a psychoactive opiate. Loperamide is simply just another opioid, it's not structurally related to morphine necessarily, but many opioids are and, and it is able to bind and have the effect that we're looking for. And again, the effect here, of course, is reward or reinforcement or or abuse liability.

29:44

A big part of this is related to lipophilicity. I've mentioned that a few times. Then I just show you here an example of the amount of brain uptake of a substance as it passes through a rat's brain after being ejected into the rat tail, and you can see that less than 10% of a morphine dose, about 30% of a codeine dose but a good percentage of heroin, because it's so lipophilic is absorbed or is transferred across the blood brain barrier directly into the brain. In the rat.

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Methadone is fairly lipophilic. But it's got different characteristics, it doesn't bind to the receptors tightly. So it doesn't have as much reward and abuse liability. It's long half life has some of those characteristics. But what you'll see what's not on this, of course, is fentanyl. And I'll put fentanyl on here for you. If we were able to do this experiment again, 50 years later, you would see that fentanyl has exceptionally high brain uptake, it's very lipophilic. And it's very easily able to get into the brain and bind to that opioid receptor, and produce reward and carry that abuse liability.

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Here are the LogP. LogP is the transformed- the log transformed value of the lipophilicity. In this case, the higher the number, the more lipophilic it is, and you'll see where a drug like morphine, I'm sorry, heroin has about twice lipophilicity of morphine, which is why it's so usable, right? Because morphine and heroin, as I said are really the same drug, right, heroin just gets the morphine into the brain more quickly. If I give them morphine into the brain, it would be like giving heroin.

31:12

Fentanyl has got exceptionally high, high llipophilicity and good binding characteristics. So it's very reward-inducing, whereas methadone, while it's lipophilic is not nearly as rewarding, although to some extent it is. And we know that and we know that people sometimes enjoy their methadone doses. Fentanyl clearly is the winner and Bupe- we think about not at all as being particularly rewarding. And that's because of another characteristic it has, which we'll talk a bit about, which is its partial agonism. All of the other drugs listed here, of course, have full agonist at the receptor, maybe not directly, as in the case of heroin has be transformed to morphine, but they are agonists.

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And here's just an example of, again, what some of these look like. And oxycodone being another one, which is has some added functional groups to it to increase its lipophilicity and make it a bit more rewarding.

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I mentioned this a little bit earlier, but you'll notice that the cocaine hydrochloride salt that we use in our noses, or shoot into our veins is pharmacologically different than the cocaine base, which we sometimes think of is freebase or much more commonly is crack. When it's absorbed into the body, cocaine hydrochloride is charged, so it doesn't get to the brain- brain very well. So even when the blood levels in that original diagram were higher, it didn't produce the same rewarding effect as the alkaloidal form, which is non-charged, and very lipophilic, and able to get into the brain very quickly and effectively. So you could see that understanding which form you're using is important.

32:46

And there are hydrochloride salts and base forms of many of the drugs we talk about. Amphetamines, phencyclidine would be examples of other ones. And even some of the opioids have salt and and base form. You think sometimes about tan heroin versus white heroin, being the basic versus the salt form of the heroin, and solubility is important because you can't smoke cocaine hydrochloride. Because cocaine hydrochloride, as a salt just, just decomposes when it's heated, whereas the base form is able to be turned into a- into a vapor, and inhaled or smoked the keep stable.

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And that's a big important difference. And you'll see that again with heroin and phencyclidine and other medications or other drugs. So the changes in pharmacological properties, while subtle, To the untrained observer, actually have really important implications in how the drug is used, and how it's abused or misused by the by the end user.

33:46

Not a lot to say about elimination, I just want to comment on some very minor aspects which probably are not directly relevant to day to day practice, but But when a drug is put into your body, it gets distributed to the organ of interest. That's the distribution half life. And then often it leaves the organ of interest and gets redistributed out into the into the body, where it goes from there is sometimes important, and I'll talk about that in a moment. And then the drug itself gets eliminated from the body even though it's no longer active.

34:16

Once it's redistributed out of the organ of interest, it still has to get out of the body. That's the terminal elimination half life, and that's sometimes described is- simply as how long it takes to get out of the body on average, but that changes over time, changes over drug use, it changes over drug dose, and that's what we use terms like apparent half life or context sensitive half life and probably the best example of that is with fentanyl. And we'll talk a little bit again about fentanyl later but recognize that fentanyl is a short acting drug. It gets into the brain really fast and it leaves the brain really fast, which is why it doesn't last very long as an analgesic. However, with continuous- I'm sorry, even in single use, even after it leaves the brain it still lingers in the body for many, many hours, right and it sits in it gets it- gets into the fat and it's slowly eliminated. So if I were to measure your, your drug four hours later, you'd still have it in your body even though the effect wore off several hours earlier.

35:14

When it's continually used, though, it builds up a lot in the fat. So the termination half life becomes fairly relative because it's so so slowly eliminated from the body. After those high doses, you actually maintain sizable blood levels of the fentanyl after multiple uses- against single use rapidly out- but long, heavy use it, it lingers and it lingers at levels in the blood that are clinically consequential so that that contextual or apparent half life can be very, very, very long for a drug like fentanyl. We expect that from methadone right? Because we know methadone is a long acting drug. But we don't expect that for fentanyl because we conceptualize the short acting drug.

36:00

We think about efficacy and I know most of you understand that, I fully expect you to- that there are a full agonist and antagonist, partial agonist... Inverse agonist is a bit of a unique concept we don't think much about but but full agonists after a dose like with fentanyl and morphine get 100%

response. Now it takes more more morphine, and it takes a longer time for you to get to 100 percent than you- then you can see with fentanyl, because it's a- morphine is less potent, so it takes a higher dose.

36:31

You'll see buprenorphine actually is fairly potent, so it takes low doses as it does with fentanyl. To some extent you can you can conceptualize the dose needed to get an effect with potency. So for fentanyl, your microgram dose... with buprenorphine, we think of sub-milligram doses. And morphine we think of multi-milligram doses to get the same effect. And that's potency.

36:52

Efficacy is a little bit harder to predict based on on those things. And buprenorphine as you know is a partial agonist. So it will never give you 100% response at the opioid receptor. What it would produce in any individual person's little variable. If we [were] just to say it's 50%, we know that at 50% of a of a full agonist opioid response, you will get some pain relief if you're opioid naive. You will get some withdrawal reduction if you're opioid dependent, but you will not get high enough levels to stop breathing like you would if you gave enough fentanyl or or morphine. So we think about efficacy as having both a pharmacological therapeutic construct and a toxicologic or overdose construct as well. Buprenorphine is a drug that's much safer to use than fentanyl, morphine or methadone, for example, because of that.

37:42

Now, affinity is where people get a little bit confused, I think. Here's a list of the affinities of all the various opioids that we think about. It is a an inverse to Ki. So it's an inverse molar relationship. So the lower the number the higher the affinity: how many moles of a drug does it take to have a 50% effect on the receptor? So with buprenorphine, it's point two nanomols whereas hydrocodone is 41 nanomols. Right. So we think of buprenorphine as having a much higher affinity than hydrocodone.

38:14

And even among the opioids, you'll see the affinities, and you can see heroin has a very low affinity compared to morphine. Thus, more that again, back to what I mentioned earlier, you have to be metabolized to morphine, for the heroin to be effective. You'll see some drugs like hydromorphone, being fairly high affinity and naloxone, of course having that affinity meaning, quote, unquote, it's able to knock off all opioid receptors, all opioid agonists from the receptor, with the exception of buprenorphine clearly, because buprenorphine doesn't have such high affinity for the receptor.

38:49

You'll hear about this in the news and we'll talk a little about some of the news stories that we read about. You can always overcome affinity unless it's permanently or literally bound to the receptor, by giving an increased dose. So there's a perfectly fine antidote for super heroin that's laced with an

elephant tranquilizer, meaning carfentanil by giving more naloxone if needed, but I'll tell you in general, since the amount of carfentanil or fentanyl in the substance is not a lethal dose, it's a therapeutic dose and I'll put therapeutics in quotes. Naloxone really works fine even for carfentanil. If you took a massive carfentanil overdose you would need more naloxone. But if you took a quote unquote, "therapeutic", maybe euphoric dose of carfentanil and fentanyl it worked fine. Naloxone works fine as you would expect it to.

39:39

Where we want to get off the rails a little bit with affinity is the concept of how it works. Affinity doesn't really mean how tightly something binds to the receptor. So I know we say it because it works for us. But when we say that fentanyl binds tighter than morphine.. when we say that naloxone binds tighter than fentanyl, it doesn't really mean that. I could... all of these things bind about the same tightness, maybe with the exception of a covalently binding, irreversible drug, but none of these drugs are that.

40:12

So when we think about affinity, what we're really thinking about is occupation, right, occupation of the receptor. Remember, drugs are always on and off the receptor. If you think about a drug, if you think about a period of time, let's just say a second, you can see a drug with low affinity might be bound for 10% of that second, and a drug with high affinity might be bound for 50% of that second. So the time that naloxone would slip on to knock the opiate or opioid off is where that opioid is not bound. So a high affinity opioid is a little harder to knock off with naloxone than a low affinity opioid.

40:46

But you can still do it because as long as that drug's not permanently bound, which none of these drugs are, you can always find enough naloxone to slip in. And once it's bound, it's governed by those same rules, and a higher affinity agonist could knock it off, which is again, why for buprenorphine, naloxone is not very effective, which raises a lot of questions, of course, about the utility of naloxone being added to to buprenorphine in the first place, and whether or not it has any unintended clinical effects, which it probably does not. But certainly the idea that naloxone could knock buprenorphine off is is a nice debate point.

41:21

Activation, of course, is governed by efficacy. We talked about efficacy, and that's partial versus full agonism. Ultimately, the combination of those two effects elicit the response we're interested in.

41:34

Okay, let's change. Let's change gears for a second, we'll talk about tolerance, or pharmacodynamics, and other pharmacodynamic effects. So tolerance, everybody recognizes the reduction in response to a drug after repeated use, right, you develop... need more of a drug to get the same effect, or you get

the same effect, you get less of an effect from the same amount of drug. So we like to say tolerance shifts the dose response curve. Remember that when we drew that curve linearly earlier, to the right, it takes a higher dose to get the same effect. And you see that here. So baseline in green, it takes 10 milligrams to get a 60% maximum pharmacological effect, whereas after using a three and a half milligrams per kilogram per day it takes... you get a 20% effect from that dose, and after further use, you get a 10% effective that dose and, and as the dose goes up, you know, obviously, you'll get more of an effect. But the concept across a single dose worked perfectly, perfectly well.

42:29

And I think everybody recognizes tolerance to see with alcohols, with opioids, you see it with other drugs. We don't see it so much with cocaine, or amphetamines. They tend to produce less tolerance, but many things induce tolerance- certainly nicotine does.

42:43

There are though, this important concept or is this important concept differential tolerance. So so the fact is that you develop tolerance, this is the same image I showed before, to analgesia at a different rate than develop tolerance to respiratory depression. Right. So you can see here that there's a linear relationship, as opposed to a more of a more of a skewed relationship between analgesia's... between respiratory depression's tolerance, and analgesia's tolerance. And the fact that that develop different rates to different extents is really important.

43:16

And that's where we come into the paradox of differential tolerance. Right? So if you think about it, if I drew this out a little bit differently here, but the, the tolerance of the analgesic effect is fairly rapid, right. And you can see that you basically, you know, develop 100% tolerance, I'm sorry, your equivalent over time, between the two of them before you start using the drug. Over time, you can see that the green line here develops much more tolerance than it does to the respiratory depressed effects. And that's a differential tolerance between pain relief and respiratory depression. What happens, of course, is that as you raise the dose of the of the analgesic opioid, of course, you develop a tolerance to it, you will surpass potentially the respiratory depression threshold for the opioid, which is why sometimes in people that are on high dose opioids, that extra pill they take at night, because their pain's a little worse than normal. Or the person who you believe has high tolerance to methadone can still overdose and die from methadone, because they hit that respiratory depression threshold, because tolerance development is very different between the two effects of the opioid. Never safe to assume that tolerance develops to all things to the same degree, or at the same rate, and this is a big important issue that we see. You know, because you say if you're tolerant, how could you overdose? And the answer is pretty clear.

44:39

Back to pharmacokinetics for a second, we think about pharmacokinetic tolerance, as I mentioned earlier, you can do you don't really see a lot of development of, of induction of alcohol dehydrogenase, but you do see development of microsomal metabolism of ethanol. So that's why

people that use ethanol heavily metabolize their alcohol more quickly. We like to think about opio-, alcohol-naive people, most social drinkers as eliminating alcohol at about 15 milligrams per deciliter in the blood per hour. Whereas over time, they're able to eliminate, say 30 milligrams per deciliter per, per hour. So they they rap- more rapidly clear the alcohol from their body, something that applies to my practice where I want to learn, remember, understand how long I should watch somebody, before I discharge them safely. We know that people who are social drinkers who come in intoxicated need a longer period of observation, and no risk of withdrawal, as opposed to people who are heavy users of alcohol because they will metabolize more quickly and have a higher risk of developing alcohol withdrawal, which is something we try to avoid developing in the emergency department.

45:44

But the pharmacodynamics are really important- what happens to the receptor. So there's lots of mechanisms here. You can desensitize GABA, and you see that here in this diagram, where you actually change the subunits within the receptor of alcohol, if you go from an alpha one to an alpha four subunit over time, or you can desensitize, say the mu opioid receptor to changing the effects of adenylate cyclase, and signal transduction or production of cyclic amp, for example, or change the receptor density of the receptors that that certain drugs or medications bind to or through internalization of receptors or reduction of the amount of receptors on the- on the neural surface,

46:24

You can also up regulate receptors. And this we see with alcohol, for example, here in this diagram, which I'll show you again in a little bit, we actually increased the amount of excitatory receptors because you've inhibited them with the alcohol so effectively, that the body wants to bring you back to a homeostatic level, you will actually increase... you will decrease the amount of inhibitory and increase the amount of excitatory receptors in response to chronic alcohol exposure.

46:51

There are other examples of tolerance, I think they're fun to mention, I'll just throw a couple out there. We think about the Mellanby effect, which is sometimes called tachyphylaxis, or Q tolerance. And that's as simple as that you can see it within a single drinking, it's the idea that you're more clinically intoxicated, as your alcohol level's rising, then you are when your alcohol level's falling at a given level. So you know, if you're drinking and you're blood alcohol levels, .08 or 80 milligrams, so you're more drunk at the beginning of the night, than after you've curved after you've peaked. And you're now back down at 80. On the way down that 80 at the beginning of the night and the 80 at the end of the night are not the same, because you've developed acute tolerance to alcohol. And that's a well described forensic effect called the Mellanby effect.

47:35

We don't talk a lot about these drugs in our world, but we think about some of the serotonergic psychedelics. People that use them will tell you that you can only use it once, then you got to wait a few days between using before you can use it again. And this graphic shows that on day one, you

need several 100 time or several 100% increase several times the amount of of LSD to get high again, on day one, and that amount falls over time. But it takes about a week, before you're able to lose your tolerance that you've developed to the serotonergic hallucinogens after a single use. And people recognize that and talk about it in discussion group.

48:12

And then we think about benzodiazepine, benzodiazepine resistance in people with with chronic alcohol use and alcohol withdrawal. We know that when we use oral opioids, we tend to induce less benzodiazepine resistance than when we use it IV. Sometimes you have to give it IV but PO is much preferred, because it tends to induce much less benzodiazepine tachyphylaxis or acute tolerance.

48:37

Condition tolerance, I think, is a concept we think about as kind of the ability to tolerate your alcohol, right? You just learned how to walk better and speak better, because you've just got so used to being intoxicated all the time. And it's classically described with alcohol, but it can be described with other drugs too.

48:53

Cross tolerance is the fact that certain drugs and medications that use the same pharmacological and neurophysiological pathways can develop cross tolerance to one another- they can they can, they can develop less responsiveness to another drug, even though that's not the drug that induced the tolerance in the first place. Right.

49:17

And this is just an example of all of the different things that bind to the GABA receptor or the chloride the GABA link chloride channel and have an effect on it. Right? And all of these develop cross tolerance. When we think about ethanol and benzos and barbs pretty easily. If I gave, say, you the dose of a benzo that I give to somebody in alcohol withdrawal, most of us would be intubated on a ventilator, but these folks soak it up, because they have cross tolerance to benzodiazepines, Just as an example, there's a lot of examples you could talk about there. It's also the reason we are able to use these medications therapeutically.

49:51

A concept that I've talked about for many, many years and I feel sort of vindicated now because the FDA a couple of weeks ago came out with a statement talking about hyperalgesia and how important it is in the, in the genesis of the opioid epidemic, right. Increasing doses of opioid lead to hyperalgesia, leading to the belief that you need more opioid, because you're developing tolerance. Right? Right. And that's basically standard development of tolerance, right where the dose required to get the same effect goes up.

50:21

In fact, opioid hyperalgesia is the other side of the coin. Clinically looking- indistinguishable- you need more drug to get the same effect. On the one hand, you could say it's tolerance to the drug's effect is wearing off. On the other hand, you could say it's hyperalgesia, the pain is getting worse. And I think recognizing that- that hyperalgesia is a big part of what we do is really important because many people who got opioids would never have developed chronic pain, had they not gotten the opioid. And the fact that we start them on an opioid leads to is this kind of rabbit hole of hyperalgesia, leading to this misguided think, thought that you need more and more drugs to treat the pain. But in fact, you probably need less and less drug to let the pain resolve on its own. Again, clinically, you can't tell the difference. Pharmacologically, you could and there are tests to somewhat differentiate some of these things. But they're not used clinically, they're mostly research efforts. But conceptually, it's important, I'm glad the FDA finally made this recognition and put a warning out about it.

51:18

Physical dependence is something we all deal with on a probably daily basis. This is the idea that you can withdraw, because you become physically dependent on on a drug. Now, dependence and tolerance are not the same thing. But they do go hand in hand. For the most part, you won't withdraw from something you're not tolerant to. Right. And for the most part, things that cause tolerance do lead to some degree of withdrawal. It's not a perfect match, but they do tend to go together.

51:43

And what is important with withdrawal is to recognize that when you withdraw, you typically just need to get back to drugs to stop the withdrawal syndrome. But that's not always true, right? We know that the E in CAGE is the eye opener, is it suggests that if you drink, you know in the morning to kind of turn off the shakes, you can still quell you withdrawal. But there is a point in alcohol withdrawal, for example, that you can't give alcohol and turn that syndrome off anymore. Right? That's the point of no return. That's when you have to start using benzos. And all the other medications we talked about, whether it's you know, propofol or etomidate a one of those other GABA ergic drugs on the receptor,

52:20

But physical dependence can occur with addictive and non-addictive use of the drugs. And caffeine, for example, is a good example. You know, many people get headaches if they don't drink caffeine, but you certainly don't think of caffeine as an addictive drug. Right? Nobody's losing their home and job over their need to treat their caffeine quote unquote, "addiction." And we use that term very loosely, of course in our vernacular, but we don't really see the psychosocial consequences of caffeine or even nicotine for that matter, and certainly not with clonidine.

52:49

Although clonidine withdrawal is very real, not very psychoactive, it's mostly a blood pressure problem, but we can still see dependence occurring.

52:57

Again, this goes back a little bit to what we talked about before with alcohol. And you can see that that what happens as you drink is you develop tolerance, so that you desensitize and increase the number of GABAergic and NMDA receptors, and you're able to, you know, very nicely get back to this new normal baseline. But when you you know, you lose inhibition, you develop this autonomic hyperactivity syndrome, which we think of as alcohol withdrawal.

53:24

The depth of dependence is also focused- related to the extent and duration of exposure of the drug. And here's just a nice example. We talked about fentanyl being short acting, you can see that even after after heavy use, you can still see that you're eliminating fentanyl in the urine for five, seven or up to even 10 days after after cessation of consumption. And that persistent bathing of the opioid receptors in that fentanyl, continually stimulating them, leads to this very deep dependence that you don't see in drugs that have short half life. So short activities in the in the blood of the brain. Right.

54:04

And that's why we think I believe that that fentanyl dependence is so much different than say heroin dependence- where you're up and down up and down several times- here you're just bathing the receptor in opioid. It's much more akin to methadone dependence and withdrawal. Although methadone is a much less potent drug on the receptor, and, you know, much less active on the receptor, I use my own word I shouldn't use it's much less active on the receptor- efficacious and it has less of a dependence-inducing effect, which is why fentanyl is just so dangerous as as a drug that we're now seeing in our drug supply. Of course,

54:45

The withdrawal syndrome is dependent a bit on how quickly that withdrawal syndrome develops. Of course, absence-related withdrawal occurs over time. Whereas precipitate withdrawal occurs very quickly, where you still have drugs stimulating the receptor, which is why the withdrawal syndrome you see from naloxone is so much worse than withdrawal syndrome you see just from stopping using an opioid. And that's probably the only real precipitate withdrawal we see is from bupe- or naloxone. Most other drugs don't have antagonists that are that effective.

55:14

There's not much to say about drug interactions. I think it's just we're thinking about the fact when you combine benzos and alcohol or, you know, stimulants, and heroin, you know, you have a speedball on the left hand side, you use the relative pharmacological differences between a stimulant and opiate, use more of both, and you sort of can can get a unique experience, but you can also quell or mitigate the effects of either of those drugs.

55:43

Of course, remember that the heroin tends to last longer than the cocaine. So when you do that- people when they do die, they die of opioid intoxication as John Candy or your your John Belushi for example. So and, and on the right hand side, the combination of two sedatives leading to enhanced respiratory and CNS depression, right, leading lead leading to that sort of drug interaction.

56:09

We think about others like the serotonin syndrome, when you can buy cocaine or MDMA, which is serotonergic amphetamine, particularly people using drugs like SSRIs, leading to this terrible hyperthermic muscle rigidity, altered mental status that we classify classically as serotonin serotonin syndrome, which you know, people can suffer from, with long term consequences, or they can die from it. So not something to be too too flippant about.

56:38

We think a little bit about some of the things we see in the media. And I just want to remind you exposure pathway, in order to- in order for that fentanyl to kill the entire population in New York and New Jersey, it has to be administered to people. So yeah, they might find 10 kilograms of drug, but it's not going to kill the whole, the whole state, because it can't get into all those people. So while maybe it's mathematically correct, it's not. It's not truly clinically credible.

57:03

And then we think about some of these exposures we see to fentanyl during during arrests- this is just a case out of California, which has been widely publicized where an officer opens up the back of a pickup truck or an SUV and see some white powder and suddenly developed symptoms and, and claps to the ground and gets better with naloxone. Clearly, he suffered from something probably related to stress. It's not fentanyl exposure, right, because even even given in a properly produced fentanyl patch formulation, after a therapeutic dose of fentanyl is not reached for about four days after transdermal application. So certainly putting a little bit on your skin, in no way cause you to collapse instantaneously. And there's many versions of this story which we could spend time talking about.

57:50

But the implications are really important to our patients, right? Because many of our many of our patients then get added things- charges. Or many of these people- not necessary our patients- have added charges like assaulting a police officer, which clearly wasn't the intent.

58:07

I want to spend a minute or a few minutes talking about clinical drug testing, I will refer you of course to the ACM document, but also to the MRO guide. I mean, it's a bit heavy, but it provides a lot of information. It's really focused on occupational drug testing for the Department of Transportation

information. It's really focused on occupational drug testing for the Department of Transportation, other organizations, but it has a lot of information that really does transfer over to our population. Remember, testing that we do is not used to catch patient-it is for DOT testing- Department of Transportation- but we're really trying to understand what our patients are doing the world, the lives they're leading, the risks they're taking.

58:38

And we have to interpret the results in the context of patients' self-reported clinical findings, life events, et cetera, et cetera. I think everybody recognizes. We don't spend time talking too much about it.

58:49

There are screening tests and there are confirmatory tests. We almost always use screening tests, in our practices, all they are are really presumptive tests. They're very sensitive, but they're not particularly accurate. They do tend to be... remember, sensitive means you're likely to find it and not miss it. But sometimes you find things that are not there. So they're not very specific. Whereas confirmatory tests are very specific, right? You're not going to find things that aren't there. You may not find everything though, right? Scre- Screening tests tend to be qualitative and easy to do. Whereas confirmatory tests are quantitative, they give you levels and they're hard to do and expensive. They go out to reference labs.

59:27

Screening tests are typically enzymatic immunoassays. It relies on an enzyme binding to a receptor binding to a drug and based on the drug structure, it's able to give you a yes/no answer. Analytical false positives are possible, meaning an opiate assay which is directed against morphine will cross react sometimes with hydrocodone. So it's analytically wrong, but it's clinically correct because you're still using opioids. But you do need to confirm positives and I'll talk about that in a moment.

59:56

Analytical false negatives are less common. In other words, the assay completely misses the analyte. But clinical false negatives do occur. So you could detect a non-morphine opioid for example. So you might detect hydrocodone, right? That is or you might detect dextromethorphan, right? These are I'm sorry, you will NOT detect those you will NOT detect the non morphine opioids. So you will not detect oxycodone, even though the person is using it. So clinically, they're positive. Analytically, it's a correct answer, right? Because the person is not using morphine. Right, and it is missing it, but it will not miss the morphine, if it's looking for the morphine

1:00:38

Often are drugs, remember, are are are unconfirmed. And they state this, and you need to be confirmed if you really want to use them in any sort of more formal way other than just a discussion generator with our patients. We think about things like the NIDA-5 or the extended NIDA-9 panels.

which we might often do and others, many of you might use a 21 test panel, some do a comprehensive panel, everybody does things a little bit differently. Probably their screening and confirmatory cutoffs that we need to think about when we do this.

1:01:11

Again, this just represents what I mentioned earlier, where you have an analyte like morphine, which is what the enzyme, the, the antibodies directed against. And because heroin and oxihydromorphone, or hydrocodone are not morphine, they may or may not find it.

1:01:26

Right, it certainly almost never find the non-morphine-like agents not morphinants, so to speak, right, such as fentanyl or methadone, because they have essentially no structural similarity. They have to have some they bind to the opioid receptor, but at least to the antibody, it doesn't really find them. But this is where it comes from, to be important to the assay. If you're looking at an assay for opiates, you're looking for morphine, right? It will not find oxycodone very well, as you can see at the end, but it'll always find morphine really well. Hydrocodone does sometimes react fairly well with the opioid assay, right? So with the opiate assay, so you will find in the second column, you will find hydrocodone cross-reacting, but in the first column it won't. You'll need fairly high concentrations of hydrocodone. Of course, yeah. And then that first column, you'll see oxycodone doesn't react at all.

1:02:16

But in the last column, you'll see the oxycodone assay. It will find oxycodone perfectly. It will find hydrocodone too, but it won't really find morphine or a number of the other opioids. Understanding the testing characteristics of your assay in your- in your practice is really important to understanding how to interpret it. And you'll see a whole list of this in many of the packaged answers,

1:02:37

I'm not going to spend time talking about each of the individual assays other than to say, the amphetamine assay is typically considered, quote, unquote, "promiscuous", because it does tend to find a number of other amphetamine-like agents, including antidepressants and some other medications, whereas the cocaine assay tends to be very good. And it doesn't find lidocaine and other things that people think it does, right? The only real false positives or clinical false positives were people using a coca tea, which contains cocaine, right, but analytically, they're correct. But clinically, they might not be because they're not using cocaine in the way we think about it.

1:03:19

Okay, so just if you were evaluating a person who tested positive for opiates on routine testing, but they tell you, they haven't used any of these medications, think about things like poppies, right, which contain morphine. So analytically, it's a true positive, they have morphine in their urine. But clinically, you're not looking for morphine, or you're not looking for this morphine, you're looking for

heroin. So technically, it's a clinical false positive, not an analytical false positive. Note, importantly, that you don't know when you get a positive opioid screen, what opioid you're finding, it does not correlate with impairment, and it doesn't tell you the root time of use or the amount used.

1:03:57

Now, if they have a negative opioid screen, It either means the patient's not using it. If you know they should be, and they're not using them, they may be diverting, it could be a clinical false negative due to collection or lab error, or you could have just used the wrong opioid assay, meaning you're looking for oxycodone using an assay that's looking for morphine. However, remember that cut-offs are often used. So even if person's positive analytically, it- they may be reported, as negative, as that result will show you or detection periods are short, right? Some of these medications might only last two or three days and you're checking in in a week, or they might only last few hours, you're checking in every day. So you have to know exactly what you're looking for.

1:04:39

The gold standard, of course, is confirmation. I don't want to spend a lot of time on this, but there's lots of these tests for it, but they all have to go out to a reference lab for the most part. And there are a ton of new opioids out there that will not cross react with the opioid assay. So all of those opioid assays that we know historically have used will be negative.

1:04:58

Now you can look at the fentanyl assay to find some of these but many of these, like the nitazenes, for example, generally won't even cross react with that. And many of the fentanyl analogues won't cross react well, either. So it's a whole Brave New World in testing, which means many of our tests have to go out to reference labs.

1:05:15

I won't say much about buprenorphine analysis, and you can certainly read through this. But just remember that we can test with buprenorphine in our patients therapeutically. And it's it, there's a bit of a science to understanding how to use buprenorphine analysis. And I detail it here a little bit for you. But it's probably more than we have time to talk about today.

1:05:34

The matrix considerations: there's lots of different matrices you can use, we think, and I'll show you a slide with some of the options, but they all have variable performing characteristics you can read on on this slide.

1:05:47

And here are some of the options like urine or saliva or hair. And they each work in some situations, and they each have limitations to use in that situation.

1:05:57

Again, another slide that just gives you some of the comparisons. It's in the slide set, I don't intend to talk about it. But it's also from the guideline that was published a couple of years ago.

1:06:07

Remember, you need to think about validity testing, whether you're measuring temperature or concentration of the urine, because there are ways that people have learned to get around some of these. I'm not going to spend much time talking about them. Many of you probably think a lot about this already. But it's important in certain patients, certain populations are always to do to validity testing.

1:06:28

So here's where you can get some help. You can ask a medical forensic toxicologist, you can ask a testing lab, you can look at the MRO certification or find somebody that has it. Certainly, I'd love to always be available to help you. And many, many of people that come from med tox background that are a big part of of ASAM and the addiction world are involved as well. So as as mentioned, here's my contact information, feel free to email me or try to contact me on Twitter. That's my twitter name, handle. Happy to talk and I appreciate all the questions. Thank you