

Key:

**J = Jason Cantone**

C = Dr. Compton

**J: Thank you for joining us. To start, can you please explain how opioid abuse affects the brain and biochemical brain processes?**

C: Opioids affect the brain in multiple ways. We think of how they have their effect on the chemicals of the brain, and that's sort of the fundamental way to consider it. Opioids are in the family of morphine chemicals, and so they have an action on the opiate receptors, or morphine-like receptors in the brain. Those come in generally three different classes, and they have Greek letters associated with them -- mu, delta, and kappa. Each of those types of receptors in different parts of the brain have different activities. The one that's most important, both for pain relief and for addiction, would be the mu opioid receptors. And they're very commonly found in parts of the brain that have an impact on reward and reinforcement, but also, they have a large number in the sleep centers of our brain. And so that's one of the complications of opioids, is that in high doses, they can cause people to fall asleep and not wake up, because they'll suppress breathing and cause people to pass out and die from an overdose.

**J: How do opioids affect perception of pain?**

C: Opioids affect perception of pain in multiple ways. Some, to some extent, they blunt this sort of emotional or response to pain. So many people describe that the pain doesn't go away, but they just don't care about it as much. So, it may diminish how important our brain thinks of the pain signal as being. But it also may diminish the actual pain signal itself, so it may blunt some of those pathways from the periphery, where pain may be occurring -- for instance after an injury to our hand -- the signals go from our hand, upper arm, through the spine and into our brains -- that's where we perceive the pain. And opioids can have an impact in multiple areas along those pathways.

**J: What is the current understanding, regarding if opioids are the best approach for treating chronic pain conditions?**

C: There's a really important question about, how do we best treat chronic pain? And for much too long, physicians have over over-relied on opioids as a potentially easy answer to pain. That couldn't be farther from the truth. Opioids are very good, short-term, at dealing with pain. So, when we have surgery, we're extremely grateful for having access to opioids during the surgery itself, and sometimes early in recovery, so that you can actually do a better job of getting back on your feet, following what otherwise would be a miserably painful experience. But opioids have complications when they're taken long-term. And so, while they may be useful and seem useful for pain, when taken long-term, they may not have the effect that we're looking for, and they don't always provide the benefit long-term that people expect or have anticipated. That's one of the traps. Because they may help you with pain short-term, but as you continue on it for longer, the complications develop further, and the pain relief diminishes over time. So, people often end up back up back where they started, or even worse, when they're on opioids for the long-term.

Now, I don't want to minimize this, because some patients do benefit from opioids when taken long-term. But the research to date suggest that long-term opioids are not beneficial on average for people with painful conditions. So, our current advice is to help people minimize their use of opioids. Try other techniques. Some of the most effective may be things like acupuncture, physical therapy -- those kind of approaches can help people with low back pain, for example. Now that said, some people will benefit from them, and when used in moderate dosages, or and observed carefully, if patients benefit, we're all in favor of reducing discomfort, reducing the morbidity and problems that people experience. And so, opioids do have a role in chronic pain. But it is much less than we thought a few years ago.

**J: Can you please go into how opioid tolerance and dependence are manifested, and how they affect the brain?**

C: You're using the word "tolerance" and "dependence" interchangeably, and I want to separate those a little bit. "Tolerance" is one phenomenon where, basically, as you use something on a regular basis, your brain adapts to it and adjusts to it. Just like when you exercise a muscle, the first time you try picking up a weight, it may be too much for you. But as you gradually use larger and larger weights, your muscles adapt and adjust, our brains adapt and adjust to the exposure to opioids the same way. So those chemicals

systems that respond to opioids actually down-regulate over time. So, as you flood the brain with opioids with pills or from medications, or from illegal sources, the brain will adapt and down-regulate the number of receptors. So that means you may need to take more of the substance in order for it to have the effect you're looking for. It's also possible that the liver, our site of metabolism of these drugs, may act more efficiently as it's exposed to drugs as well. So, there are different ways that tolerance can develop.

That's different from the term "dependence," which can be related to both that phenomenon of tolerance, but it's also related to the withdrawal syndrome that people experience, when they abruptly stop or diminish the dosage of an opioid that they've taken for some time.

**J: Speaking of that, how do brain abnormalities result differently after opioid dependence, versus addiction?**

C: There's a really important way to distinguish. Anybody that takes opioids on a regular basis is at risk for withdrawal symptoms. If you or I are prescribed opioids following a very serious medical procedure for a number of days, and then those medications are stopped suddenly, we may not feel very good. We may have an upset stomach, have trouble sleeping, have craving for the medications, also be quite cranky and irritable. You can be hard to live with when you're going through a withdrawal. Now after just a few days like that, the withdrawal symptoms generally are mild, and quite self-limiting. But if somebody's been on opioids for weeks, months or years, those symptoms can be quite significant, and require medical treatment. And the best approach is to reduce the dosages of the opioids extremely slowly to minimize those. Because one of the big risks that happens is, when people experience that with those withdrawal symptoms that have been described as being very similar to a serious flu, when they're -- and we know how bad you feel when you have the flu. It's that level of discomfort and complication. Generally, not life-threatening, but a very serious health condition when you go through a withdrawal.

When you experience that, one of the things that you may do is want to go back to the dose of the medication that prevented that. And that's why when somebody has been on these medications, or taking them illegally or illicitly, we want to reduce the dose slowly over time.

**J: How do stress and other environmental effects affect the brain and the use of opioids?**

C: It's a remarkably complex relationship of stress to the use of opioids. First off, "stress" is a very broad term, and it can include everything from the stress of a difficult childhood environment, the stress of difficulties at home, to the physical stress when you have an illness. You know, we were just talking about having the flu, and how withdrawal can mimic the flu. Well, if you get sick with the flu, your body's under great stress, and you feel great discomfort. So, stress comes in all those different ways.

But in general, opioids can both be a response to stress -- so what puts people at risk for starting down that pathway of using opioids, and then liking them and using them excessively, may be extreme life stresses, or physical stresses, across many years. But we also think about the importance of stress during recovery. When somebody has quit using opioids, and they're clean and sober, one of the main risk factors and problems is when they're under extreme stress, partly because of a learned behavior, and partly because of the automatic response of the brain when the chemicals that are involved in a stress response are released, they make drug use appear even more appealing.

**J: There's been much attention paid to the biological basis of the disease. Recent thinking, and NIDA-funded research, says there is a heavy influence of social interaction on addiction. Has there been a change in the way research has been approached?**

C: One of the difficulties in doing research is to try to figure out how to look at combinations of factors. As a researcher, I always want to separate things out and just look at one thing at a time. You know, I'd like to look at genetics. I'd like to look at how things run in families as an example of genetics. I'd like to look at how a medication has an impact on somebody, just one at a time. But it turns out that isn't the way our patients operate, and that's not the way the real world operates. And so, what we've begun to do is, have a more sophisticated view of how to examine combinations of factors simultaneously. So how might our medications that we know are useful for saving lives, and helping people enter recovery, how do we look at that in combination with the essential nature of social support, social interactions -- frankly, helping people get back to their full interactions with families and with friends and at work? That's what we mean by living a life. And it's those combinations of those interactions among these factors that are difficult to study, but probably will be the most fruitful in terms of our understanding how to help people in the long run.

**J: How do currently approved pharmacotherapies for opioid use disorder work?**

C: We're very fortunate in this field that for opioid use disorder, I have three medications I consider for a patient with this addiction problem. We have the full agonist -- that's methadone. And I'll explain what I mean by "agonist" in just a moment. We have a partial agonist, that's buprenorphine, and then we have an antagonist -- that's naltrexone. All three of these medications operate on the opioid receptors in our brain.

So, the antagonist is probably the easiest to understand. We have these receptors in our brain, and by using this medication, we fill those receptors with this medication, naltrexone. So, it fills the receptors for opioids. So, if an exogenous, an external opioid, comes along, somebody takes an oxycodone tablet in order to get high -- guess what? The receptors are already occupied by something that blocks their activity, and so nothing happens. I like to explain that if my patients relapse while they're on an antagonist, they end up with an empty wallet, a sore arm, and no high. And so there may be a learning from that. And then they learn that there's no reason to go down that pathway. So that's basically how an antagonist, like naltrexone -- naltrexone can be provided in a pill that somebody takes every day. But a recent advance, just a few years ago, was a monthly injection -- that's very helpful. It's hard to take pills every day. You have to be motivated and interested, and a once-a-month injection means you're covered for an extended period of time without having to make that decision on a daily basis -- all right, is this the day I'm going to stay clean and sober, or not? So that's a very helpful addition to our treatment armamentarium. Now that's the antagonist.

Buprenorphine and methadone are both substitutes for opioids. So essentially, what they do is, they provide a way to stabilize our opiate receptor systems by filling them with active medications. Methadone is a full agonist, so it operates just the same way morphine and other opioid agonists do. But by providing it in a regimented way, especially when given in an oral manner, by mouth, it doesn't produce the intoxication or high that injection or smoked opioids will provide. And by filling the receptors with an agonist, it actually means that when people use drugs on the side -- and they will, our patients will test the limits, even if they want to remain clean and sober, people have lapses -- they won't get high from using it. That's the key for all of these, is preventing the triggers for long-term use, by influencing whether they get high or intoxicated when they will slip.

Buprenorphine is a different medication. It's a partial agonist. So, it has both activities, like morphine, like the other opioids, and it has a partial antagonism effect. It's a little unusual. So, if somebody's intoxicated on heroin or fentanyl, or oxycodone and you give

them buprenorphine, you'll actually put them in withdrawal. Because it partly blocks the effects of opioids, to a degree. But it also occupies them and produces some activity at those opioid receptors. And so it can act a little bit like the pain medications and like methadone, in terms of filling them with an active medication, but it still reduces the relapse by helping people not experience the intoxication they're looking for, if they do slip. These medications also block withdrawal symptoms, and that may be a key component. Withdrawal is not the only reason people use these drugs, but it is a major reason. And so, by preventing them from having withdrawal symptoms, they're much less likely to reach out for the substance that they know can relieve their illness or their discomfort.

**J: Can you please explain how Narcan works, and how it is administered?**

C: Narcan is a short-acting antagonist. Narcan is the trade name for a medication called naloxone. And naloxone has been used in medical settings for many years. So, if you come into an emergency room with an overdose, so you're unconscious and blue, you're not breathing, one of the first things they'll do is administer naloxone in an attempt to wake you up. Because if you have overdosed on an opioid, this medication, when it gets into the circulation, enters the brain, it'll push the opioids, the active things that are stopping your respiration centers from working, it'll push them off of those receptors and take their place. So, it's kind of like glue for those receptors in the brain. And like a sticky glue, it'll fill them up, and the chemicals that would produce intoxication, or respiratory depression, can't have their activity.

Naloxone is short-acting, though, so it only works for either a few minutes up to a few hours, depending on the dosage. The good news is that it can be administered intranasally -- that means we can spray naloxone into your nose, and it actually will get into your brain just as fast as if I gave you a shot with it. So, an injection into your muscles is about the same speed of entry into the brain as a nasal spray. That was one of the discoveries and the developments in the last few years that we did at NIDA, and working with a pharmaceutical company, to develop an easier-to-administer form of naloxone that then could be readily used in community settings, by family members, by friends, by police officers and others, who may encounter somebody who's overdosed. It's all well and good to have a rescue medication available in an emergency department, most people may not make it to the emergency department. Because if you stop breathing, we only have a few minutes to get that reversed before there's permanent damage, or death.

**J: Are there known individual and environmental factors that influence whether people who use opioid drugs will eventually become dependent or addicted?**

C: That's a terrific question. Who becomes addicted? What explains people developing a problem with opioids? One important factor to keep in mind is, I can describe risk factors which put people at higher-than-average risk. But I can't completely explain why every person will become addicted, because the chances are that some people may become addicted that have none of these risk factors. And that means that addiction can strike any family, somebody from any background, and with any psychological or biological predisposition, or not. So, you may be at lower risk, but you're never at zero risk. So, I think that's an important thing to keep in mind.

What does put you at risk? Well, one of the obvious factors is, it runs in families. If you have family members with heroin addiction or opioid addiction, especially close relatives -- that means parents, siblings, or children with these conditions -- you, yourself may be at higher risk. A prior history of another substance use problem is also a major risk factor. So, one of the things I look for is, all right, I've got a 35-year-old who is going to be started on opioids for a medical condition. Are they at risk for developing problems? They have some risk inherent to anybody who's exposed, but are they at higher-than-average risk? Well, if they have a history of tobacco use earlier in their life, or a history of heavy alcohol consumption -- these are very common conditions, especially during late teens and early twenties. They may have recovered from it, but if they have that in their background, guess what? Their brain may be predisposed to developing problems from the opioid medications themselves. So that's one of the important factors when it comes to the onset of these conditions.

We could also describe other ways that people are at risk. What's available in your neighborhood? What's available in your environment? What was your early childhood environment like? People who come from very difficult environments early on may be predisposed to finding substances particularly appealing, and opioids will be part of those. That's kind of a general risk factor for all substance use, misuse and addiction, but it applies to the opioids as well.

**J: What do judges, specifically, need to know about the biology, neurobiology, and chemistry of opioid use disorder?**

C: What we can do is combine the strengths of the public safety system -- that's what judges represent -- you're going to help us keep criminals off the street, and keep me safe from people that are committing crimes, as well as the public health and treatment

community. And it's by working together, actually, that we can improve both outcomes. That's been one of the tricks here, and the important factors here, is that by providing treatment to people who have addictive disorders who happen to be in the criminal justice system, we can sometimes reduce the likelihood of criminal problems, as well as, of course, help their health and social outcomes. So, there may be many reasons for judges to be knowledgeable about this, to help improve the outcomes that judges care most about, which is public safety and social factors. But by learning about these health issues, and by doing a better job of making sure that the offenders that you all interact with are getting the care that they can benefit from, it may turn out -- won't always turn out -- but it may turn out that we help the very outcomes that you're most concerned with as well.

**J: Is there anything else our viewers should know?**

C: Sometimes judges are reluctant to consider methadone or buprenorphine as opioid agonists, or partial agonists, in the treatment of offenders with an opioid use disorder. And I understand that reluctance, because in some ways, these are replacement medications. They do have activity at the opioid receptors that are at the heart of causing the problem with opioid use disorder, or opioid addiction. So why would we use a replacement treatment? Well, the data is incontrovertible, that these medications can save lives and help people recover and turn their lives around, in terms of re-entering society as productive members of the community. And so, I rely on the evidence to help guide our decision-making about what medications to consider for our patients.

In the meantime, at the National Institute on Drug Abuse, we're looking for better solutions that will be longer-term, and maybe get at the fundamental nature of addiction itself. All of these treatments for opioid use disorder, in some ways, are patches; they help people get their lives back in order, but they aren't getting at the underlying nature of addiction. They are treatments to treat the symptoms and the problems. And we hope to engage in research that will one day provide the answers that we all seek.