Ruth Adewuya, MD (host):

Hello. You're listening to Stanford Medcast, Stanford CME's podcast where we bring you insights from the world's leading physicians and scientists. This podcast is available on Apple Podcasts, Amazon Music, Spotify, Google Podcasts, and Stitcher. I am your host, Dr. Ruth Adewuya. Welcome to season four of Stanford Medcast. This episode is part of our opioid miniseries. In this episode, I am talking with Dr. Anna Lembke. Dr. Lembke is a professor and medical director of addiction medicine at Stanford University School of Medicine. She's also the program director of the Stanford Addiction Medicine Fellowship and chief of the Stanford Addiction Medicine Dual Diagnosis Clinic.

Dr. Lembke received her undergraduate degree in humanities from Yale University and her medical degree from Stanford University. Dr. Lembke's pioneering efforts have had profound implications on public health. Recognized as an early voice in the medical community, she was pivotal in raising awareness about the perilous consequences of opioid over-prescribing and the ensuing opioid epidemic. Leveraging her platform as a Stanford University School of Medicine faculty member, Dr. Lembke has cultivated an array of impactful educational initiatives. She has spearheaded innovative teaching programs focusing on addiction, the art of safe prescribing and pioneering strategies for opioid tapering. Thank you so much for chatting with me today, Dr. Lembke.

Anna Lembke, MD (guest speaker):

Thank you for inviting me.

Ruth Adewuya, MD (host):

You are one of the first in the medical community to raise concerns about opioid over-prescribing in the opioid epidemic. What were some of the early signs you noticed?

Anna Lembke, MD (guest speaker):

In the early 2000s, I started seeing patients coming in who were addicted to the opioids that their doctors were prescribing. And that was something that came out in discussions about other addictions that they were struggling with, where they would begin to talk about how they were misusing the opioids given to them for pain in order to change the way they feel, or to get high, or really just to target pain. But now we're taking their opioids in risky and dangerous ways. I do remember very vividly a woman who we were treating for depression and anxiety whose son died from a prescription of methadone that was given to him by his pain doctor. It wasn't for an opioid use disorder, it was for pain.

And this was very early on her sense that the doctor had really harmed her son, because she had repeatedly gone in and said, "Hey, this is not going well. I'm very concerned about the way that the methadone is impacting him, the possibility that he might be addicted, that he's been addicted in the past," and the doctor's brushing her off and ignoring that and then finding her son deceased on his bed in his childhood bedroom in her home, and just the devastation that she experienced from that. So, those were the types of anecdotal or clinical phenomenon that we were seeing, some very early signals starting around 2001, 2002.

Ruth Adewuya, MD (host):

The story that you mentioned, very devastating and sad in terms of the posture of the medical community to the issue. I wonder, from your perspective, why do you think it took so long for the medical community to recognize the scale of the crisis?

Anna Lembke, MD (guest speaker):

I really do believe that doctors were duped into believing certain myths about opioids when prescribed for a patient with pain. This is a wholesale campaign that captured medical education beginning in the late 1990s. It was initially spearheaded by well-intentioned doctors, primarily in the pain community and the hospice community, who felt that we weren't doing enough for people at the very end of life, for people with terrible pain syndromes. And they were absolutely right. But what happened is that messaging got hijacked by the opioid pharmaceutical industry. And then once there was all that money behind it, it became really like a sea change or a cultural paradigm shift. And at the vanguard of that was this miseducation of doctors, telling them that as long as they were prescribing the opioids for a patient with real pain, that somehow that patient was going to be immune.

The teaching then was that it was like a biological phenomenon, that actually the pain was literally somehow biologically protective for that individual and they couldn't get addicted to those opioids, or at least it was very rare. And that word rare was used often, as it turns out totally untrue. It's common for patients with pain to get addicted to the opioids their doctors are prescribing. About 20 to 30% of patients with chronic pain being prescribed an opioid will misuse that opioid. And about eight to 12% will develop an opioid addiction. And that's according to World Health Organization standards, that's common to very common, not at all rare. But I think it's easy to look at the opioid epidemic and say, oh, it wasn't prescription opioids. And of course, right now, it's primarily not prescription opioids and it's a list of fentanyl.

But early on, it was primarily prescription opioids. It was prescription opioids that were leading to addiction among pain patients and then also massive diversion. So, an increased supply broadly in the community such that non-patients were getting access. But mostly it was initiated, sparked, propelled, propagated by well-intentioned doctors who thought they were doing the right thing by prescribing opioids to patients with pain who were taught to believe that they couldn't get addicted, that no dose was too high. The patient came in and had developed tolerance just to go up on the dose or add a short-acting opioid, and on top of a long-acting opioid, on top of a transmucosal opioid, et cetera, et cetera, till we ended up with a whole generation of patients on these massively high doses. And then, of course, we're still suffering the consequences of that.

Ruth Adewuya, MD (host):

Those numbers of eight to 12%, really staggering numbers, till we really reflect on what that means in terms of the number of people that will be impacted by this. But even though it has now evolved to other pathways for the opioid crisis, it does seem that the medical community will need to play an important role in being part of the solution to this. I think it speaks to the healthcare system too, how we've used the term misinformation all the time when it came to the COVID-19 pandemic and how people who were not clinicians were saying all of these things. But clearly, clinicians are not immune to this misinformation, miseducation, especially when there's the backing of a whole marketing campaign targeted towards clinicians.

Anna Lembke, MD (guest speaker):

Absolutely. First of all, I agree with you that if there is a silver lining to be found in this tragic opioid epidemic, it's that it has forced the medical community to pay attention to the problem of addiction. And for the first time in 200 years, we are beginning to build an infrastructure inside the house of medicine to target and treat addiction, something that prior to the opioid epidemic we never did. But the other big piece of this is that conditions were and continue to be ripe for this misinformation about opioids in the medical community. Because of our dysfunctional healthcare system, which is very poorly

equipped to help people with chronic relapsing and remitting disorders that have a psychological or psychiatric component.

We're really good at getting in there with unclogging carotid artery or replacing a hip or a knee. We're terrible at dealing with the kinds of chronic illnesses that are biopsychosocial in nature, that require slow medicine and time, both in the short and the long term. And the quick fix is usually the wrong fix. And that would be chronic pain, as well as addiction and other mental health disorders. So, the kinds of misinformation that was propagated, it's a tribute to the Sacklers and Purdue Pharma, and the genius of their marketing campaign. But it's also true that doctors were for this kind of misinformation, because they were desperate to have something to do to help their patients in pain, especially primary care doctors who were absolutely overloaded with huge patient panels, 10 minutes to see very complex patients. And then all of a sudden someone says, "Hey, you can prescribe OxyContin and no dose is too high." Of course, people are going to jump at that.

Ruth Adewuya, MD (host):

Although there are general guidelines around the education that you should engage in, it's basically a self-identification for the clinician to seek the education that makes sense for their timing. One of the things that you alluded to earlier was this idea of individuals who are receiving opioids for legitimate medical reasons, can still be trapped in this addiction cycle. What do you think are some factors that contribute to the transition from appropriate pain management to this problematic opioid use?

Anna Lembke, MD (guest speaker):

We have really good data on that. And two of the biggest factors are simple dose and duration. So, the higher the dose and the longer the patient is on an opioid, especially if they're on a high dose opioid for a long duration, the more likely they are to experience problems including the problem of addiction. Which is why the CDC guidelines have emphasized really as their headliner, that if you're going to use opioids, use them at the lowest dose possible for the shortest duration. Other risk factors for somebody who's prescribed an opioid for pain to develop an addictive disorder is a co-occurring mental illness. So, that's not really surprising. We've known that for a very long time.

But that speaks to the importance, not necessarily of withholding opioids in that population of opioids are medically indicated, but just recognizing that's a higher risk group. Other risk factors or the typical socioeconomic factors that are predictors of addiction risk more broadly, things like being unhoused, unemployment, living in poverty, multi-generational trauma, things like that, those are some really concrete things that we have good data around that people can look out for. But I think even bearing that in mind, it's important to realize that a person with none of those risk factors can still get addicted to opioids prescribed for a bonafide medical condition.

Ruth Adewuya, MD (host):

And why is that the case? What about the potency of opioids contributes to their addictive potential?

Anna Lembke, MD (guest speaker):

The thing about opioids is that they work on the pain system, but they're also working on our dopamine reward pathway. It's more than a dual function. They have many functions working on many different kinds of systems. But the key here is that a person can get potentially short-term pain relief from an opioid. That's not all that it's doing. It's also leading to increased dopamine release in a dedicated part of the brain called the reward pathway, which is, of course, the very circuitry that's involved in the

development of addiction. Over time, the individual can develop a tolerance, not just to the pain relieving effects, but also to the other psychological or psychotropic effects, such that they need more of it over time.

As they escalate dose, their body and brain then compensates by downregulating opioid receptors, downregulating dopamine transmission. And then you can get into the addiction vortex complicated by the pain vortex, where now it feels like you're having more pain, but really you could just be in withdrawal from the opioid, which is often characterized by physical pain even in people who don't have pain conditions. So, you have this almost double helix of pain and opioid addiction spiraling together in a way that just can be very hard to tease apart and can be very difficult to get out of.

Ruth Adewuya, MD (host):

And for clinicians, what are some of the signs that they should be looking for to identify if a patient may be addicted to opioids?

Anna Lembke, MD (guest speaker):

It's super important to track the hallmarks of misuse, because misuse is the on-ramp potentially for addictive use. I always like to emphasize that misuse is not the same thing as addictive use. You can have somebody who's misusing their prescription opioids. And if you identify it early and enter with some corrective measures, that person might well be able to change their behaviors around how they're using their opioids. But if you don't, then it can progress to full-blown addiction. I think maybe a good thing to do here is just define addiction. Addiction is the continued compulsive use of a substance or behavior to spite harm to self and, or others. And importantly, that's sometimes harm that the patient can see and sometimes harm that they cannot see, which is why it's so important to not just use the subjective account of the patient as the only data point by which to measure whether or not that patient is running into problems with their opioid.

It's really important to get collateral information from friends and family, from urine toxicology, from the prescription drug monitoring database, from the rest of the medical records. There's a really wonderful study that was done by the Kaiser Family Foundation in patients who have chronic pain who take opioids, asking them if they were developing a misuse or an addictive use problem. I'm not remembering the numbers exactly, but something like a quarter of them thought that they might be developing a problem, which by the way is a high number, a quarter of those patients. But if you talk to their family members, about 50% of their family members thought that they were developing a problem. You have this interesting gap between people able to observe the problem themselves, versus other people who are able to observe it in them, which is just really important to take into account.

So, the things to look for are things like early refills, demanding higher doses, especially after dose escalations have just been done. The patient's spending a lot of time, energy and effort trying to get more opioids. Sometimes that's doctor shopping, going around to multiple providers looking for the same or similar prescription. Sometimes it's just a lot of calls into the clinic, talking to nurses, elaborate tales about prescriptions having lost or stolen. So, these are the things to look for, and you're looking for a pattern. Patients really can have their prescriptions lost or stolen, but if you're seeing a repeated pattern of it, it's very concerning.

The other thing to look for is evidence, again, of things like doctor shopping on the prescription drug monitoring database, or for example, combining benzodiazepines with opioids, which is sometimes what people do to augment the high or just its risky combinations that would be a form of misuse or a red flag to look for. Again, talking to family members, super important. And then also, I think it should

be standard of care to just flat out ask patients questions like, are you hoarding and binging on your pills? Are you creating a stockpile so that you can take more all at once? Are you taking them other than prescribed or more than prescribed? Have you ever done something like crush and snort your pills, or crush and inject your pills?

That might sound extreme, but that's the kinds of problems that people get into when they're developing an opioid addiction. And so, I think it should be standard of care to just flat out ask anybody to whom you're prescribing an opioid, how are you doing with the pills? And you can normalize it by saying something like, "It's quite common for people even who have serious pain disorders and are getting opioids prescribed by their doctor for pain to run into problems with that, and here's some of the problems that we see. Are you experiencing any of these?" And then just go through the list, as well as, of course, collateral information and checking your periodic checks of the urine drug screen and the prescription drug monitoring database, which the CDC now recommends that we do quarterly.

Ruth Adewuya, MD (host):

You talked about some of the signs that clinicians can look for when trying to assess whether someone is addicted to opioids. Let's talk about the overdose piece. Can you talk a little bit about why an opioid overdose is life-threatening?

Anna Lembke, MD (guest speaker):

Sure. So, opioids also work on the brainstem. And they can lower heart rate and lower breathing rate, such that over time an individual who combines an opioid that even if they're tolerant to it, the tolerance to the pain relieving effects happens faster than the tolerance to the respiratory suppressant effects. So, as dose goes up, those respiratory suppressant effects increase. In fact, at the height of the prescription opioid epidemic, when we started looking at hypoxemia in patients on high dose long-term opioids, we were seeing a whole cohort of individuals who were walking around with not enough oxygen in their blood. And then combine that with a little bit of obesity and a little bit of sleep apnea. And then maybe something like even as seemingly benign as gabapentin added to it, a GABAergic calming neurotransmitter type of drug, and that might be enough right there or a single 12 ounce bottle of beer, or something to just put that person into essentially overdose mode where they fall asleep, stop breathing, their heart stops and they don't wake up again.

And that's usually how it happens. The idea of opioid overdose is a bit of a misnomer, because many of these individuals who have died from prescription opioids have not taken more than prescribed. They've taken it just as prescribed, but again, over time they've needed higher and higher doses. And just being on a high dose puts people at increased risk of overdose. And we have lots of data on that now, showing that an opioid at any dose has risks. But if you go above 50 morphine milligram equivalents daily, you begin to see significantly increased risk of "opioid overdose." And above 90 morphine milligram equivalents, it goes even higher. It's not a dichotomized thing, it's a graded or gradual thing.

With all increasing doses, the risk of overdose goes up. And then again, combining with it a muscle relaxant or a benzodiazepine or a GABAergic drug, then you're increasing the risk of overdose, even beyond that. So, that's how it happens. Of course, some people intentionally take more than prescribed to relieve pain, or to get high, or to go to sleep or what have you. That's not the most common case. The most common case seems to be these "accidental overdoses," which again, at the height of the epidemic around 2012, 2013, probably wasn't even more than prescribed.

Ruth Adewuya, MD (host):

Are those numbers different when you're talking about the synthetic opioids?

Anna Lembke, MD (guest speaker):

A lot of different things go into making an opioid addictive. Potency is one of them. Now, morphine milligram equivalents accounts for potency. So, it's like a way to convert any opioid to a common currency. In synthetic opioids, that just means they're made in a laboratory. So, what you have is naturally occurring opioids that are derived directly from the poppy plant, like opium or thebaine. Then you have the semi-synthetics, which start with a poppy plant, but then add some laboratory manufactured moiety to make it into a new compound. That'd be something like buprenorphine. And then you have the fully synthetic opioids. Those are ones that don't even need a poppy precursor. They're made entirely in the laboratory. That would include something like fentanyl.

Now, fentanyl is exceptional because it is so incredibly potent. It being synthetic, means that it's also cheaper to make because you don't need to plant a field of poppies. But what really stands out about fentanyl is that it's potency, it's about 50 to 100 times more potent than morphine. Which means that a tiny little bit, especially in somebody who's opioid naive, is enough to kill. And it kills, again, that same way that this respiratory suppression occurs at about the same level that pain relief occurs. So, it's a dangerous drug. It does have a pharmaceutical utility. It's used all the time in a perioperative setting. It is used in hospitalized patients with severe pain who need a very potent opioid.

But the problem is that now you have a whole industry, a whole market for this legally manufactured, largely imported fentanyl that's mixed into other opioids like heroin or even other additives, making things like counterfeit pills, something that looks like a 10 milligram Percocet, but actually has nothing but fentanyl in it because fentanyl is so cheap, plus like Lamictal or some other inner ingredient. So, you have people who can take one counterfeit Percocet and die from that. And of course, we're hearing about that tragically all the time, because it has fentanyl in it. And that's enough to kill them, because they're not opioid tolerant.

And then, of course, you have the scenario where people get addicted to opioids, and so over time they need more and more potent forms to get the same effect. So, they're actually seeking out fentanyl, and smoking fentanyl, and injecting fentanyl, and doing that intentionally because they need the more potent form because their body has adapted to the less potent forms. And those individuals are, of course, very high risk category, because getting that titration just right is very difficult to do.

Ruth Adewuya, MD (host):

I'm overwhelmed by the challenge and the interconnectedness of all of the issues around it. In the appropriate setting, people need to be able to manage their pain accordingly. So, it's not something that you can say, just stop making it and be done with it. And then all the other factors that you layered on top of it affecting the opioid crisis, it just seems like such a complicated and challenging issue to navigate. And then opioid withdrawal and the feeling of the withdrawal causing physical pain, and choosing to avoid that discomfort makes people not want to go through their process. What are some practical approaches to managing and supporting individuals through opioid withdrawal?

Anna Lembke, MD (guest speaker):

We've learned a lot in the last five to 10 years about how to do that. I think managing withdrawal was for decades really the domain of addiction medicine doctors, addiction psychiatrists, but now we see many more people who have skills in that area out of necessity, obviously. So, one of the things that we have learned collectively as a field is that patients with chronic pain who have been on opioids for a long

time, especially at high doses, are going to need a lot of support in getting off of them, and that a slow taper for many of these individuals is best. And by slowing the taper down, what we can do is mitigate some of the withdrawal effects and make it a more manageable humane process for those individuals.

When I say slow taper, I'm talking in some instances years. So, for patients who have been on opioids for years, it is reasonable to assume that they will need some years to get off of it. And that some of them might be able to get to a certain dose, but not ultimately get all the way off, that they may have to be on some maintenance dose. Not necessarily because it's good for their pain, but just because their brain has been changed so much by exposure to the opioid that a maintenance of a lower dose may be the least risky strategy for them. And that to try to get them all the way off can be potentially riskier than the risk of keeping them on a low dose chronically.

The other great tool that's come out is a medication called buprenorphine, which is an opioid, but it has certain unique properties. First of all, it has a ceiling effect on respiratory suppression. So, it doesn't lower the heart rate and the breathing rate as much as full agonist opioids. And therefore, it tends to be a safer opioid. It's harder to overdose on it. And then secondly, it also has this very long half-life, so that people can get into a steady state of their dosage level and then experience some relief from the constant fluctuations of shorter acting of full agonist opioids. And so, we found that it's a very helpful medicine, not just for opioid addiction, but also for people with opioid dependence and complex chronic pain who need a maintenance opioid to manage those dual syndromes.

Ruth Adewuya, MD (host):

It's really great to hear that there are alternatives that are available. Are there any non-opioid pain management approaches that can be utilized instead of any type of opioid?

Anna Lembke, MD (guest speaker):

Absolutely. So, there are other medications, other pharmacologic strategies that are alternatives to opioids. And there are non-pharmacologic strategies that are alternatives to opioids, and that's all the mind-body work, psychotherapy, Feldenkrais, physical therapy, acupuncture. We don't have a whole lot of evidence, honestly, around non-pharmacologic strategies, in large part because there's not a big industry supporting studies on those. There's the orphans of medicine generally as the psychosocial interventions, which is too bad. Because in the long haul, my guess is that those are the interventions that are going to ultimately be most effective for patients with chronic pain.

As far as non-pharmacologic strategies, as far as other pharmacologic strategies, really important study that came out showing that in patients with chronic pain who were followed out for a year, that in fact opioids worked no better than Tylenol and other pharmacologic interventions, but that opioids were associated with more medication related to adverse events. So, that was a very useful study, because it really did show that if you're going to use a medicine for chronic pain, it probably shouldn't be an opioid. That it doesn't work any better than Tylenol, it's associated with more harms. But frankly, even Tylenol didn't work all that well for chronic pain for a year out.

So, the messaging there is unfortunately, the state of the art, is that we don't have any good medicines to treat chronic pain. And a study just came out recently, in fact, showing that even for acute pain, like acute knee and low back pain, opioids aren't better than non-opioids. Which is important, because of course, opioids for acute pain can be a gateway to persistent opioid use, which then can be a gateway to addictive use. So, any way we can shield people from the harms of opioids is a good thing. And sometimes that means you using non-opioid alternatives instead of opioids, even for acute pain.

Ruth Adewuya, MD (host):

In your book, Drug Dealer, MD, which by the way, what a fantastic title to have for a book.

Anna Lembke, MD (guest speaker):

In your face.

Ruth Adewuya, MD (host):

It's right there.

Anna Lembke, MD (guest speaker):

At the time it was necessary. I don't know that today it would be.

Ruth Adewuya, MD (host):

The issue was still with us. So, I think that it's worth looking at. But in that book, you conducted extensive interviews with a variety of healthcare providers and journalists. And you really tried to talk about the relationship between doctors and patients. You talked about the science of addiction. From your conversations, what were some of the barriers that you saw that were hindering us from addressing drug dependence and addiction?

Anna Lembke, MD (guest speaker):

One of the biggest barriers at that time was the shaming of doctors who did not do "everything within their power to help a patient in pain." There was really this ethos that anybody who called out the prolific opioid prescribing as a potential harm, was somebody who was going to deny a patient with pain access to the thing that would relieve it, was going to be the person who was not willing to do anything about our "national pain epidemic." And that was probably one of the biggest factors that I saw. Because what I would see in my interviews with doctors and cases that we saw, even in patients who had obviously developed a full-blown prescription opioid addiction, doctors were still reluctant to stop prescribing, because they were worried that they would be negatively called out for not providing "pain relief." Or even actually sued, because in that time period, especially that first decade of the 2000s, doctors and nurses were being sued if they didn't relieve their patient's pain.

So, it was fascinating at the time and also in retrospect for me to see how there can be this cultural hegemony that develops in medicine around whatever it is. But at that time, it was around the need to prescribe opioids to anybody in pain. And that's essentially what the culture was. And it's hard to imagine, but that's really how it was. If you weren't willing to prescribe it, there was something seriously wrong with you. You were like a sadistic human and a terrible doctor. So, that was the culture and very hard to escape that.

Ruth Adewuya, MD (host):

I want to end our conversation going back to where we started and the role of the medical community in this crisis, and how in some way was the incubators where this thing grew and now it's expanded. What role do you believe medical professionals should play, should continue to play in this ongoing issue of the opioid crisis?

Anna Lembke, MD (guest speaker):

Just looking back at my own professional life, when I trained at Stanford Medical School and started my residency, I really thought that all I had to worry about was just taking care of patients one patient at a time. But I really have shifted on that. And although I think being a good clinician is paramount, I've also come to believe that doctors need to be more aware of these systemic problems, and actually speak up and advocate for change where they see flaws in the system. Because the system is so giant now and we're so captured by it, the vast majority of doctors now work for an integrated healthcare system, were salaried employees. Very few doctors are out there just hanging out their shingle working for themselves anymore. We're literally unionized in some cases. So, we have to look at how these systems aren't serving patients and really advocate for change on that front. And that goes for the way we prescribe opioids, as well as anything else that happens in medicine.

Ruth Adewuya, MD (host):

You've been incredibly generous with your insights. And I know that, as we mentioned, it's a complex issue with nuances to each of the questions that I've asked you. So, I very much appreciate you taking the time to chat with me today.

Anna Lembke, MD (guest speaker):

It was my pleasure. I actually haven't talked about this in a while, and so it was fun.

Ruth Adewuya, MD (host):

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