40| The Effect of Opioid Use and Treatment on Cognition – With Dr. Monica Rivera Mindt

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Monica Rivera Mindt, Ryan Van Patten, John Bellone

Intro Music 00:00

Ryan Van Patten 00:17
Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior. I'm Ryan Van Patten...

John Bellone 00:24
...and I'm John Bellone. Before we get into today's episode, we wanted to announce two new exciting projects that Ryan and I have been working on. One of

them is directly related to NavNeuro. We realize that our episodes are fairly lengthy and we like to really dive into topics and let conversations unfold naturally, but we know that it may be a lot of content for our listeners. So within the next few months, we are going to have a new type of episode called Neuropsych Bites. These episodes will be much briefer, 15 to 20 minutes, and much more narrowly focused. We'll tell you more about these very soon.

The second project is a book that Ryan and I are writing about becoming a neuropsychologist, which will include advice and guidance for students and trainees who are interested in pursuing a career in neuropsychology. It's going to be like a blueprint students can follow. The idea for this came from emails that we received from students asking about how they might go about becoming a neuropsychologist and there really wasn't any one concise resource that we could point them to. So we decided to write the book on it. We already have a contract with a major publishing company and the book is set to be released by the end of 2020. The reason why we're bringing this up now is because we want to ask you - whether you're a high school student, or a college student, or a grad student, or even a seasoned neuropsychologist - we want to ask you if there is anything that you think we should cover in the book that we might not have thought about. Any questions you have that you'd like us to answer in the book. Please email us at feedback@navneuro.com with those questions that you'd like us to weave in.

And now for today's episode, we brought Dr. Monica Rivera Mindt back on. She is a board certified neuropsychologist. She is also a tenured professor at Fordham University in New York City, and has an affiliation with Mount Sinai as well. You might have listened to Monica's last episode with us on cultural neuropsychology, Embracing the Mosaic that was episode 21. We would highly encourage you to go back and listen to that if you haven't yet. This is going to be a completely separate conversation about opioid use disorder, how it relates to cognition, and also treatments for it.

Ryan and I are going to give a little bit of an overview. You want to get started Ryan?

Ryan Van Patten 02:38

Sure. So we really get into the weeds with Monica, but in order to offload some of the background and statistics from her, we'll present those here to prime you for what's coming. So opioids can be synthetic compounds such as fentanyl or methadone, they can be semi-synthetic such as hydrocodone and oxycodone, or they can be natural such as codeine and morphine. The CDC emphasizes that

prescription opioids are an effective treatment for certain types of short term pain. But there are great risks to using this type of pharmacotherapy in the long term, for example, for people with chronic pain.

Here are a few stats from the CDC related to the opioid crisis in the US. In 2013, 249 million prescriptions were written for opioid pain medications. If that number didn't land on you, keep in mind that there are only about 330 million total people living in the US right now. The estimated economic costs of the health care crisis is approximately $78.5 billion per year. The National Institute on Drug Abuse estimates that more than 130 Americans die of opioid overdose each and every day. Adding to that, approximately 21 to 29% of patients prescribed opioids for chronic pain ultimately misuse them. Between 8 and 12% develop an opioid use disorder. An estimated 4 to 6% who misuse prescription opioids end up transitioning to heroin or other harder drugs. And about 80% of people who currently use heroin first misused prescription opioids.

John Bellone 04:37

There was a 2019 paper in JAMA open network - we're going to link to all these papers that we're mentioning - but that 2019 paper showed that, in 28 states, the mortality rates from synthetic opioids more than doubled every two years. It appears that the epidemic has progressed in phases. The 1990s and 2000s were characterized by prescription painkiller use. 2010 through now saw an increase in heroin use, and 2013 through about 2019 saw an increase in synthetic opioids. From 1999 to 2016, a total of about 231,000 men and about 120,000 women died from opioid-related causes across the United States. And opioid-related deaths in the US have increased more than four folds during an 18 year period from 99 to 2016.

Ryan Van Patten 05:26

From the same paper, they also reported compelling data that the opioid-related mortality rates are disproportionate across the US such that mortality is higher in the eastern US compared to elsewhere. This is not due to differences in overall use in the east compared to the west, but it relates to higher potency drugs in the east such as fentanyl. People may have seen headlines a few months ago that opioids now kill more Americans than motor vehicle accidents.

John Bellone 05:57

That's saying a lot. The CDC released a guideline for prescribing opioids for chronic pain. Again, we'll link to this, but it's directed towards primary care physicians.

There are 12 guidelines with three overarching principles that drive the recommendations. One of the principles is that non-opioid therapy is preferred for chronic pain outside of active cancer, palliative, or end-of-life care. Things such as physical therapy, physical exercise, cognitive behavior therapy, and non-opioid medications like NSAIDs, non-steroidal anti-inflammatory drugs. Another principle is that, when opioids are used, prescribers [should] prescribe the lowest possible effective dose in order to mitigate the risk of addiction and overdose. And then the third principle is that healthcare providers should exercise caution when prescribing opioids and should monitor their patients carefully. And, again, this is directly from the CDC.

Ryan Van Patten 06:54
And not from the CDC, but another potential treatment in order to reduce opioid use that I've come across would be medical marijuana. Again, there's not a lot of research on medical marijuana as an opioid sparing strategy, but there's some promise with that. And, along those lines, John and I will be releasing within a few months a full episode dedicated to recreational/medical marijuana and the impacts on cognition and emotion, so stay tuned for that.

To end our introduction, I'll run through the DSM-5 criteria for opioid use disorder. First, taking more or for longer than intended; unsuccessful efforts to stop or cut down; spending a great deal of time obtaining, using, or recovering from use; experiencing cravings; a failure to fulfill major role obligations due to use; continued use despite resulting social or interpersonal problems; important activities reduced due to opioid use; recurrent use in hazardous situations; continued use despite resulting in physical or psychological problems; and, of course, the hallmark physiological symptoms [of] tolerance and withdrawal.

John Bellone 08:19

Maybe we should quickly explain what those mean. So “tolerance” means that you need more and more of the substance to get the same effect as before. And “withdrawal” means that when you stop using the substance, you experience symptoms.

Ryan Van Patten 08:30

In the DSM-5 compared to the DSM-IV-TR, the floor for symptoms required to diagnose substance use disorders was lowered such that now it is only required that two to three symptoms from the previous list I just read be present in order for mild opioid use disorder to be diagnosed.

And, finally, as a public service announcement, some recent news was announced on NPR on February 26 of this year. After a long legal battle, a Philadelphia-based nonprofit organization called Safe House is opening the first supervised injection site in the United States. This is a big win for harm reduction advocates. And it's relevant to our current episode because we end up talking to Monica a fair amount about treatments for substance use disorder and opioids, which include harm reduction techniques. For those of you who may be interested, we will include a link to the NPR article in our show notes.

John Bellone 09:34
And, now, we give you our conversation with Monica.

Transition Music 09:37

Ryan Van Patten 09:37
Monica, we are thrilled to have you back on NavNeuro. Thanks for coming back to the show.

Monica Rivera Mindt 09:51
Thank you so much. It's wonderful to be here again with you two.

Ryan Van Patten 09:54
So let's start with some basic terminology. The overlap and differences between the words "opioid" and "opiate" can be confusing to people. My understanding is that “opiate” was traditionally used to refer to natural compounds derived from opium poppy, such as morphine and codeine, while “opioid” was used to describe more synthetic drugs that act in the same receptors as opiates, such as fentanyl and methadone. But these days, it seems like the word opioid is used to refer to both natural and artificial compounds. I'm curious what lingo you prefer.

Monica Rivera Mindt 10:31
We tend to use the term “opioids”. So I think that's what we should go with today.

Ryan Van Patten 10:36
Okay, easy enough.

John Bellone 10:37

We've already provided our listeners with some relevant stats in the intro, but would you please give us a little bit of an overview of the opioid epidemic? How it got started? The evolution of it?

Monica Rivera Mindt 10:50

Absolutely. Well, first of all, it's important to note that the epidemic is both based on prescription opioids and illicit drug use, like heroin. Often the epidemic is pinpointed as starting around the 90s or so, is what I would say when we typically think that it started. In terms of changes in use, that's absolutely true. But I'm going to take more of a sociohistorical perspective and take us back a little further to 1980. Because, really, the crisis arose in part because physicians were told that the risk of addiction and dependence was low when opioids were prescribed for chronic pain. In fact, I don't know if you've heard about this one-paragraph letter that was published in the New England Journal of Medicine in 1980, but what it says, towards the end, is something to the effect that "we conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction." And so this very small paragraph that appears in 1980, then by the 1990s, becomes invoked over and over in support of this claim that prescribed opioids for management of pain is safe and there isn't a risk of dependence. There's a great piece on this actually in a 2017 article by Leung and colleagues, not surprisingly, in the New England Journal of Medicine.

But, essentially, the way that this whole epidemic begins is through this confluence of pain management advocates and oxycodone marketing. This was very much the result of what happened from an economic perspective in the United States. I always tell my students, if you're trying to understand something, follow the money. If you want to understand this public health crisis with the opioid epidemic, same thing. So we have this confluence of pain management efficacy and oxycodone marketing that is successful and truly too successful in one way, because it ended up with this massive change and the increase in opioids that were dispensed by pharmacies. You know, up until 1990, it had been low and steady, but then certainly by the late 1990s and into the 2000, there was this tremendous steep increase in oxycodone, and then the use of prescribed pain medications.

For those of you who are interested, this all comes from, in many ways, the Sackler family, which they're the founders of Purdue Pharma, and you might have heard their name because they've been in so many legal battles recently in the press, they're coming out a lot. So Purdue Pharma is behind Oxycontin, and this hits the market in about the mid 90s. Between 1995 and 2003, Purdue was selling almost

$2 billion worth of Oxycontin annually. I know several people where this was their gateway into difficulties and opioid use dependence. Now the Sackler family is worth about $13 billion, but they're also embroiled in extensive legal battles with numerous contingents including a massive lawsuit with a group of more than 500 cities, counties, and tribes.

John Bellone 14:10
And then fentanyl comes on the scene a little bit later and causes more problems after that.

Monica Rivera Mindt 14:16
Yeah, absolutely. So fentanyl has been a big driver in the steep increase in overdoses that we've seen. For those of you who aren't really well aware of fentanyl, fentanyl is a very concentrated and deadly form of synthetic opioid. It's about 50 to 100 times more potent than morphine and it's cut into heroin and other illicit substances like cocaine, methamphetamine, counterfeit opioid analgesics and benzodiazepines. It's really lethal.

Ryan Van Patten 14:50
Often you don't know what you're getting, obviously, with the street drugs. They can be cut with many things and fentanyl is a particularly bad one to be taking and not know you're taking because it's so very potent.

Monica Rivera Mindt 15:03
That's exactly right, Ryan. So it's been such a dangerous evolution of what's been going on with opioids in the United States. This is really taken the overdose mortality rate [and] just made it skyrocket since especially I think about 2013 or so.

John Bellone 15:22
Are there any socio-demographic groups that tend to be most affected by the epidemic? Who's most vulnerable here?

Monica Rivera Mindt 15:28
Certainly, it affects all segments of the population. Now it includes younger and older populations. It affects men, women, transgender, non-binary persons, and people of all races and ethnicities in the United States. I think that earlier on people had an idea that it might affect one group more than the other but that's just not the case anymore. It's really spread at such a rampant level, it's hard to keep up with.

Although I will note that there are some important geographic variations in the rate of drug deaths related to opioid use. So, for instance, the highest overdose rates in the United States are actually clustered in the Appalachian mountain range, the rust belt, and New England. In certain places, the way in which people use these substances could be more or less dangerous. For instance, people, I believe, are more likely to die from injecting heroin than from smoking it.

Ryan Van Patten 16:28

That's a pretty good segue into the neurobiology of opioids - the pharmacodynamics. We know that they tend to increase dopamine in the mesolimbic reward pathway, as do all drugs of abuse, but this is a very simple model that's common across different substances. Can you add a little more nuance and depth to the neurobiology of opioids in particular?

Monica Rivera Mindt 16:51

Sure. So let me take a step back. When we think about opioids, you're absolutely right, we're thinking about the reward pathways - we think about dependence or addiction. That all starts with thinking about positive reinforcement and how those behaviors get reinforced. So humans, like other animals and organisms, engage in behaviors that are rewarding, and that pleasurable feeling that they get provides positive reinforcement so that behavior is repeated again and again. We have natural rewards - endogenous opioids, for instance, but also opioids like heroin and others. So in terms of their action in the brain, essentially once - I'm going to use heroin as an example. Once in the brain, heroin is converted to morphine by opiate receptors in certain areas of the brain. So they bind to opiate receptors especially concentrated in areas within the reward pathway, including the ventral tegmental area, VTA, the nucleus accumbens, which people think about a lot when we think about reward and pleasure, and also the cortex. It also binds in the pain pathways, which include the thalamus, the brainstem, and the spinal cord. When we're talking about that pain pathway, opioids are related to analgesia as well. But when we think about the biological mechanisms, certainly we're thinking about the ventral tegmental area especially as being important because it's the origin of the dopaminergic cell bodies and the mesocorticolimbic dopamine system and other symptoms. So it's widely implicated in the effect of drugs like opioids in the neural circuitry.

John Bellone 18:41

Do we know if there are particular regions that are more vulnerable to being damaged by this process?

Monica Rivera Mindt 18:48
You mean by opioids?

John Bellone 18:50
Yes.

Monica Rivera Mindt 18:51
Sure, sure. I think that there, again, we're talking about lots of brain regions and circuits that are involved. So certainly, the frontal lobes, prefrontal cortex and subcortical structures are involved in what I just mentioned. Certainly the basal ganglia regions and the hippocampus have been implicated as well.

John Bellone 19:17
So it's not just that there's an increase in dopamine...

Monica Rivera Mindt 19:19
Yeah, no.

John Bellone 19:20
...through the mesolimbic pathway. It's also potentially the mechanism of harm for some of these neighboring structures.

Monica Rivera Mindt 19:27
Absolutely, absolutely.

Ryan Van Patten 19:29
Opioids are not the only drugs of abuse that have the potential to hijack our brain's reward system, of course.

Monica Rivera Mindt 19:36
Right.

Ryan Van Patten 19:36
The comparison that I've made is to psychostimulants - you know, cocaine and amphetamines - which are very addictive as well. So my question harkens back to your description of the history. I'm wondering why it might be that opioids in

particular compared to amphetamine and cocaine have become such a big problem when both types of substances can hijack our reward system.

Monica Rivera Mindt 20:02

That is such a good question. For me, and, again, this is just my opinion, but I really think it was a toxic convergence of market and social forces all at once. Again, we had big pharma really pushing opioids and oxycodone and Oxycontin, and at the same time we also had this movement in terms of pain management, again, which is really important. We, as neuropsychologists, physicians, and allied health professionals need to be thinking very seriously about positive and healthy ways to approach pain management. But I really think it was a toxic convergence of these different forces in our culture.

Ryan Van Patten 20:46

Yeah, that makes sense. So I'd like you to talk for a few minutes about common pathways to addiction in opioid use disorder. Obviously, for each individual, they have their own story and set of circumstances. But a common story that I've heard about people is, in particular, a pathway to addiction through prescription opioids is someone breaks their leg or some other orthopedic injury, goes into the hospital, and then their acute pain is treated with opioids. They're taking it for a while, they get out of the hospital, they go home, they continue to take it. Maybe this person happens to have a genetic vulnerability to addiction, which may or may not have been known already. Maybe they get an extra prescription and/or they have a friend of a friend who is able to get them a little bit more on the street, and it just becomes this spiraling, like downward spiral. I've heard that that's a common story. But what's your take?

Monica Rivera Mindt 21:46

I absolutely agree with you. Again, I think it's so easy to think about this through the lens of the “other” - that this happens to other people, but it's affecting so many Americans in the United States. I think most people know at least one person who has been touched or affected by this. In my personal and clinical experience, very often the story that you mentioned is very much the trajectory I've seen. People have suffered from some sort of physical injuries, maybe a sports injury or a work-related injury. In fact, what I've heard from people in rural areas is that people, you know, in doing farming, often their gateway into opioid use problems has been through having a work-related injury on the farm and then getting prescribed these pain medications and that it just goes from there. But also sports injuries, I think, are a real unfortunately common gateway for people as well. For others, certainly, it

can be self-medication for other types of psychiatric comorbidities. Even when we think about how young this epidemic is hitting, you know, kids in high school or maybe even middle school, which is really hard to even get our heads around, it's experimentation. There are multiple pathways. But certainly prescribing practices have been a big piece of this puzzle. Once individuals are exposed to those medications, they are much more susceptible. But you're also correct that it's a complex interplay. Not everybody who tries opioids once is going to evolve into having an opioid use disorder. It's a complex interplay between biology and the environment. A number of genes have been identified as making individuals more susceptible to dependence but that interacts with a number of environmental factors, including, again, as I mentioned, comorbid psychiatric issues or trauma, stress, comorbid substance use, and really even just the availability of the of the substances themselves in the environment.

Ryan Van Patten 23:59

I think we can transition now into intervention. I'd like to talk about harm reduction for a few minutes, Monica, if that's okay with you. So this is a policy of providing safe methods for drug use as opposed to more strict criteria of full abstinence, harsh measures, such as we had in the “war on drugs” in the US in the 80s and 90s. Harm reduction includes techniques such as distributing clean needles and syringes to prevent the spread of HIV, providing safe spaces for consumption, and distributing the opioid antagonist naltrexone. Harm reduction programs are active in Europe and in other places and there's some political support to implement them in the US. For example, I've seen in the news some talk in Pennsylvania, but there's no legislation that I know of to actually implement harm reduction in the US. I'm curious, broadly speaking, what your thoughts are on this approach to treating substance use disorders and what you think might happen with harm reduction in the future in the US?

Monica Rivera Mindt 25:02

Well, I want to be very clear and upfront that I am a big proponent of harm reduction techniques. There is a strong body of evidence to support harm reduction. And as a neuropsychologist dedicated to evidence-based treatment, I think that there are a lot of reasons for us to change our policies here in the United States to adopt a more harm reduction approach. I appreciate the way you framed the whole concept of harm reduction, because you're exactly right. It reduces the harm for people not seeking or able to get treatment. It really focuses on reducing the consequences related to substance use. It's important to note that abstinence is

not a prerequisite to care and so really [it's] meeting people where they are. In terms of the evidence, it's really overwhelming.

There are different types of harm reduction approaches. One type is opioid agonist treatment and medication assisted treatment, which uses opioid agonist treatments like methadone and buprenorphine. They're related to significant declines in HIV, hepatitis C mortality, and other besides health-related outcomes that are extremely important. Also other types of outcomes, for instance, reduced re-incarceration, as well as less transmission of communicable diseases. So there are a number of reasons why we should be having a very active conversation about harm reduction and why it's not an integral part of the approach to handling the opioid use crisis in the United States.

Ryan Van Patten 26:47

We're going to talk more about the opioid agonists and partial agonists that are used before we get into methadone and buprenorphine. For listeners that aren't familiar, this doesn't make sense. Can you talk about why one treatment is an opioid antagonist, another one is an opioid partial agonist, and another one is an opioid agonist? [laughs]

Monica Rivera Mindt 27:07

[laughs]

Ryan Van Patten 27:07

I can see why people might not understand why those can all be treatments in different ways.

Monica Rivera Mindt 27:12

Right. So let me talk about agonists first. There are two types of medications that we routinely think about when we talk about opioid agonist treatment. Those would be methadone and buprenorphine. Methadone, its mechanism of action, basically works as a full opioid agonist. Maybe I should take a step back and we should talk a little bit about psychopharmacology for a second. So opioid analgesics can act through three different types of opioid receptors - mu, delta, and kappa. So methadone is a full opioid agonist on the mu receptor just like heroin or other things. Another medication, buprenorphine - its commercial name is Suboxone, but I'm going to talk about its medical name buprenorphine.

John Bellone 28:11
Sorry. I've also heard it referred to as “Bupe”. [laughs]

Monica Rivera Mindt 28:13
Yeah, yes, yes.

John Bellone 28:14
That's what the kids are calling it.

Monica Rivera Mindt 28:16
Yeah, that's what the cool kids call it. [laughs]

Ryan Van Patten 28:18
[laughs]

Monica Rivera Mindt 28:18
Yeah. So buprenorphine is a partial opioid agonist but it's also a kappa antagonist. So it has two different mechanisms of action. Then a full other type of antagonist would be Naloxone or naltrexone, which is used actually as part of the harm reduction armamentarium as a way to block the effects of opioids and can be used in terms of overdose.

Ryan Van Patten 28:50
So we use the antagonist as a life saving device to prevent an overdose, whereas we're using the partial agonist and agonist as a replacement for the opioid - the treatment, right? Which can be like long-term maintenance or a tapering downwards. Is that accurate?

Monica Rivera Mindt 29:07
That's exactly right. Thank you for that clarification. Again, when we're talking about opioid agonist treatments, we're talking about them as medication assisted treatments. These are FDA-approved medications and they're meant to be used in combination with counseling and other behavioral therapies to provide treatment for the whole person in the context of substance use treatment like this. I think that they have received some concerns because some people have said that they substitute one drug for another, but that's not it at all. These are really important treatments. These are medications to relieve withdrawal symptoms and psychological cravings that cause chemical imbalances in the body. And MAT

programs really provide a safe and controlled level of medication to overcome the terrible consequences of opioid dependence. Research has really shown that this is a safe and important and effective approach for treatment.

John Bellone 30:10
Do we have a sense of how long people usually stay on the maintenance therapies? Is this an indefinite sort of therapy?

Monica Rivera Mindt 30:17
Good question. I think that it's important to think about opioid use disorder as being a chronic condition. So, you know, we think about diabetes as a chronic condition, or hypertension as a chronic condition. People don't typically have any problem, at least in terms of stigma, with taking their insulin or taking their hypertension medication to deal with these chronic conditions. However, because of the stigma related to opioid use, getting the uptake for people to gain access and utilize medication-assisted treatment has been very difficult and to our detriment as epidemiological studies and the rate of overdose in this country shows. This is a really important tool for people to utilize in the long term. There are ups and downs in treatment, but there are also ups and downs in treatment of diabetes and other chronic illnesses. I think that we, as neuropsychologists and allied health professionals, need to think about it more in those terms, so that we can be of better service to our patients.

John Bellone 31:24
Right. Obviously, this is much better than using heroin or something else. Ideally, though, someone would transition eventually off of the maintenance therapies completely, is my understanding.

Monica Rivera Mindt 31:37
Yeah, they absolutely could. But these medications can be used in the long term. People can transition off and sometimes go back on. But, again, I think if we think about this in a broader context, as a health-related disorder, it's really a neurobehavioral health disorder, right? We can think about treatment in a much broader spectrum, rather than treating it once for this very finite period and you're done.

John Bellone 32:03
I like that model. And I like your diabetes analogy. Someone might be on metformin for the rest of their life, or with exercise and with losing weight, they might actually

get to a point where they don't need metformin anymore. And, you know, they could go on it later if they needed it. I like that analogy.

Monica Rivera Mindt 32:19
Well, thank you.

John Bellone 32:20
Do we know if there are any impacts of these maintenance therapies on cognition?

Monica Rivera Mindt 32:26
There are. So again, I've already talked to some about the benefits of these medications in terms of outcomes. Before I move on to cognition, I just want to note that there has been quite a bit of research for outcomes with regard to methadone and some with buprenorphine. Really, in terms of reducing mortality, high risk behaviors, HIV transmission, improving physical and mental health, reducing criminal activity, improving quality of life and social functioning, again, there's a lot of evidence for why these treatments merit systematic inclusion in the armamentarium of treatments that we consider.

In terms of the effects of these treatments from a cognitive perspective, let me take a step back. There have been a number of studies, many more of them have been with methadone rather than buprenorphine, but overall what the literature suggests in general is that healthy controls tend to perform better in terms of cognition than individuals who are treated on these medications. I'm going to say OAT, opioid agonist treatment. People treated with opioid agonist treatments, or OAT, tend to perform better cognitively than active opioid users. So there is some nuance there. In terms of the longitudinal findings, what I think is really exciting is that with both people who use methadone or buprenorphine, both of these groups demonstrate improvement in cognition over time overall. So that's really positive. In terms of methadone versus buprenorphine, cross sectionally I think that there's probably enough literature to suggest that people on methadone can perform as well cognitively as individuals who are just abstinent on opioids. But with regard to longitudinal findings, some studies show that people on methadone perform better in terms of processing speed, learning, memory, and executive functioning.

There's much less research with regard to buprenorphine though, which is unfortunate. I'm just going to briefly put the buprenorphine research in context, as well, to just note that much of the work that's been done with buprenorphine has been done in Europe with mostly homogeneous populations. In general, both

abroad and here in the United States, we don't have a lot of information about these types of medications in terms of diverse populations. And really not that much about women. So I'm talking about this in broad strokes in terms of the cognitive effects, but there are limitations to this literature as well. So with that caveat, I will say that buprenorphine has also been associated with improved attention/working memory, improved executive functioning. A couple of studies have shown that individuals on buprenorphine performed better than methadone, particularly in terms of executive functioning and attention and working memory. But again, we don't have that many studies, and not many in the United States to work from, and most of them have been cross sectional. So we need more work to flesh out and better understand the effects of buprenorphine and methadone on cognition.

Ryan Van Patten 35:49

Thanks for reviewing some of this literature. That's really helpful. I'd like to ask about the mechanism in terms of cognition and substance use broadly. I think it's easy for me and other people who are initially thinking about this, to assume that someone is taking a drug of abuse and then that drug causes their cognition to decline. We see that people who use cocaine, or marijuana, or opioids have worse cognition than those who don't. So it must be that the drug is causing it. That's one potential explanation. Another potential explanation is that people who have some cognitive inefficiencies or impairments are more at risk to use initially. So the cognitive impairment came first. It could be going in one direction or the other. Of course, these are not mutually exclusive - both could be happening at the same time. People who have cognitive impairments could be at risk for drug abuse. They have worse executive functioning and planning, they're more vulnerable, etc. and actually using and abusing the drug could impact the brain such that it negatively affects cognition. Do you think the literature in substance use disorders broadly and then opioid specifically is developed well enough to answer this question about directionality?

Monica Rivera Mindt 37:10

I don't think so. I think you hit the nail right on the head in terms of this whole notion of chicken and the egg because I do think that there probably are some cognitive vulnerabilities at play or predilections certainly. We do have quite a bit of research that does show that there are significant acute and chronic effects of opioid use. So that is certainly clear. But I do think that there is a little bit of a chicken and the egg going on here. The research has been useful in showing some of the effects of opioid use on the brain in terms of the specific mechanisms.

John Bellone 37:50

Yeah, and those mechanisms are also still up in the air in terms of what specifically causes the damage. I've seen, overall, people who have opioid addiction have cortical atrophy - their ventricles are enlarged relative to the non-opioid using population. I think it's still unclear, that's my understanding, as to what's specifically underlying that change.

Monica Rivera Mindt 38:15

I think that's true. But there is some research that also shows that there are - you know, I think there's a lot to work out. We do know that neurovascular disorders are implicated in opioid use. Leukoencephalopathy is also present in opioid use as well. So, that can be part of the puzzle where we see involvement of white matter. This actually tends to be the case more for inhaled opioids like heroin rather than an injected drug use. As you mentioned, absolutely, atrophy related to frontal lobes, basal ganglia, and the hippocampus is also implicated in terms of the effects. But the specific mechanisms, I would assume, there is some neurotoxic injury going on here. But I think that is still being worked out.

John Bellone 39:09

Do we know if the frequency or the dose or age of onset or duration of use - do we have a sense of whether and to what degree these affect the cognitive presentation?

Monica Rivera Mindt 39:22

Well, certainly, I think some of the most compelling research that I've seen is the frequency-dose interaction. The more frequent and higher the dose. There is some good research on that combination negatively impacting cognition. Also the age of use at onset. I think the younger the age has also been shown to impact cognition in terms of worse outcomes. That really sticks with me in terms of prevention and intervention at an early age to help reduce the impact and negative sequelae associated with opioid use disorder.

John Bellone 40:03

We have this developing brain...

Monica Rivera Mindt 40:05

Absolutely.

John Bellone 40:06
…that could be extra impacted.

Monica Rivera Mindt 40:08
Yeah, absolutely. I think that's a really important and interesting area of work, especially a jumping off point for interventions and prevention, which we need to be thinking about as well.

John Bellone 40:21
You mentioned the substance use comorbidity - other substances, alcohol, cocaine, they're commonly used in addition to opioids. Do we know if there are additive effects? I mean, it seems obvious that there would be on cognition.

Monica Rivera Mindt 40:36
Absolutely. For anybody who has worked with people using opioids, it's very rarely the case that they're only using opioids, right? I gave a talk not too long ago and I was in a big room of people and asked everybody to raise their hands - you know, how many people have only worked with somebody who exclusively used opioids. And there was not one hand raised.

John Bellone 40:59
I was at that talk. [laughs]

Monica Rivera Mindt 41:01
Yes, you were. Yes. [laughs] And so, this is true. Clinically and in terms of my research, that's been my experience as well. Certainly the most common comorbid substances that I've seen used with heroin have been alcohol, cocaine, and cannabis as well. So those are some of the biggies in terms of the additive effects. There is also research to suggest that there are additive effects. In fact, our group conducted a study that was published in 2016, in Addictive Behaviors, the first author was Franchesca Arias, who's now at Harvard. Our study back then showed that comorbid alcohol dependence was related to significantly worse global cognition, executive functioning, motor functioning, verbal functioning, and processing speed. So there was quite a pervasive negative impact of having comorbid use. We also found that comorbid cocaine dependence was also significantly related to worse executive functioning and motor functioning. So, yes, these things don't usually happen in isolation. When we're working with individuals,

either with regard to research or clinically, working with people with opioid use, we also have to be very mindful about comorbid substances and alcohol.

John Bellone 42:27
It seems like they have an additive effect specifically on the white matter. You mentioned kind of like a subcortical sort of profile.

Monica Rivera Mindt 42:34
Yes, absolutely. I often think about somewhat of a frontostriatal presentation when I think about this.

John Bellone 42:41
Yeah. Processing speed, executive functioning, attention.

Monica Rivera Mindt 42:44
Exactly.

Ryan Van Patten 42:45
So we've established that opioids impact cognition and the brain. It would seem obvious that neuropsychologists have a role to play in the care of people who struggle with this. And yet my experience suggests that, at least in psychology, we don't often think of neuropsychologists as being frontline to help with people with substance use disorders. There are other psychologists who do that, right? I haven't talked to a lot of neuropsychologists who frequently see patients who are referred to them specifically for substance use disorders in general. It could be just based on the settings that I've been in, but what role do you see the field of neuropsych playing in the opioid epidemic?

Monica Rivera Mindt 43:28
I am so glad you asked that question. Thank you so much because I strongly believe that neuropsychologists - again, neuropsychologists are brain behavior experts and we're talking about a neurobehavioral disorder. And just to throw some cognitive domains out there, there was a recent meta analysis conducted by Wollman and colleagues back in 2018 that showed large to medium effects of chronic opioid use on complex psychomotor functioning, attention/working memory, memory, visuospatial functioning, and then small to medium effects for executive functioning. So here we have a disorder that's related to several cognitive domains and somehow neuropsychologists are not an integral part of care. I believe that this

strongly argues for how we can be doing better with regard to how we handle the opioid crisis in general. And neuropsychologists, in my opinion, need to be key leaders, both in research and in clinical treatment. Especially if we think about treatment for opioid use as a chronic condition that needs integrated care, right? We have a strong body of evidence that shows that this is a cognitive disorder, to a great extent, and we need to have experts in this area to help inform evidence-based approaches so that we can utilize cognitive profiles to tailor treatment.

John Bellone 45:04

Yeah, absolutely. And just to summarize or clarify, it sounds like this would also be helpful for people on maintenance therapy. So although the cognitive deficits are greatest in people who are actively using opioids, to a lesser degree the similar cognitive impacts occur with the maintenance therapies as well. Right?

Monica Rivera Mindt 45:27

They can.

John Bellone 45:28

They can. Okay, that's a good clarification.

Monica Rivera Mindt 45:29

They can occur. But, again, what I think is most important to focus on is that people improve over time with opioid agonist medications. But neuropsychologists can be there to assess cognitive function at baseline, and then to monitor progress over time and to inform the team about the best approaches for, for instance, medication adherence. If somebody is going to be going with buprenorphine as their treatment - I didn't mention this before but in terms of the difference between methadone and buprenorphine, one of the great benefits of buprenorphine is that it can be taken at home. A person doesn't have to go into the clinic every day to receive their medication. They can just go to the pharmacy and get a prescription like you would any other medication and take it at home. So medication adherence then becomes an important issue, right? We know that cognition is strongly related to adherence, we have lots of evidence for that. We can also, as neuropsychologists, be of service in integrated care teams when we also think about other mitigating risks from a harm reduction perspective. So if we know that somebody is at greater risk to engage in risky behaviors, like future injection drug use or risky sex practices, because they have perhaps poor executive functioning, we can work to create tailored recommendations to mitigate those risks.

John Bellone 46:53
So in our role on those integrative teams, when exactly do you think testing would be helpful? If the person's actively using still, is that a waste? Or should you wait a certain period of time after abstinence from opioids?

Monica Rivera Mindt 47:09
There are a lot of different opinions about this, and I respect the people who have these different opinions. I think reasonable people can look at the evidence and come away with different conclusions. I would say that so long as a person is not acutely intoxicated, I think it can be helpful to engage in at least some form of cognitive testing, if for nothing else to establish a baseline prior to treatment. Again, taking this harm reduction approach, I don't think that we need to have somebody perfectly adherent on treatment or abstinent to start trying to understand their cognition because there's so much that we can gain from understanding where they are at the moment, in terms of their cognition, to help inform treatment.

Ryan Van Patten 47:56
Well, I'm sold on the utility of neuropsych in this population.

Monica Rivera Mindt 48:01
[laughs] Good. Good.

John Bellone 48:01
Wasn't a hard sell for Ryan. [laughs]

Monica Rivera Mindt 48:02
[laughs]

Ryan Van Patten 48:04
Then my follow up question would be: imagine a psychologist at a hospital who's not seeing any of these patients, but knows that in their clinical environment certainly there are patients with opioid use disorder and/or who are on maintenance therapy. What do you suggest we do as an individual practitioner to start to bring in these referrals? Like, should we suggest that PCPs administer the MOCA and then refer to us their patients who have substance use problems? Should we be reaching out to substance use clinics or other psychologists? What do you think is a good approach?

Monica Rivera Mindt 48:40
I'm going to use a trick from improv. I'm going to take an "and both" approach. I think that we're dealing with a public health crisis right now. It's all hands on deck right now. What that means is, I think, that we as neuropsychologists have to partner with our physician colleagues, our registered nurse practitioner colleagues to inform them about the role of neuropsychology in substance use treatment, the cognitive risks for people who are utilizing opioids. I think that administering the MOCA is a safe and feasible option in terms of implementing some sort of cognitive screener in an integrated care type of environment. But, I also caution that that does not count for a neuropsychological evaluation. It's just to, perhaps, flag that there is an issue that merits further assessment.

At the same time, I think that for neuropsychologists and for everybody who's seen that patient, or a research participant in any context, we all need to start asking about opioid use. I think that part of the trick here is that we're seeing somebody in a particular clinic. Maybe it's in a clinic for a chronic disease like diabetes, again, going back to that, or hypertension, general internal medicine clinic or what have you, somebody is being seen for depression - whatever the point of contact, I think we all at least need to start asking. Especially when we're working with older adults or very young, you know, minors, younger people, and everybody in between. Because oftentimes, people present for one problem but they could also be experiencing problems with opioids and they might be too embarrassed to even bring it up. Again, as neuropsychologists we can be leaders, we can inform those that we work with, and we can partner with folks to figure out the best ways to approach assessment and treatment.

John Bellone 50:42
Regarding the test battery, or the interview, the neuropsych eval, is there anything unique about these types of evaluations relative to the normal assessment?

Monica Rivera Mindt 50:53

I think that in terms of the clinical interview, it's important to get a very comprehensive timeline. So ask questions about substance use history and create a follow back timeline where you're getting lots of information about when they were using. Thinking both - what we talked about before actually, John - about frequency and dose, to get a sense. And certainly age of onset, that can also inform our working hypothesis about what might be going on with an individual. I think you can start the clinical interview at that point, really taking an in depth approach. Definitely

doing a formal evaluation to diagnose opioid use disorder for DSM criteria or whatever criteria you're using.

Then when we get to the point of the actual neuropsychological test battery, I would always recommend a comprehensive battery because, as I mentioned earlier, there are so many different domains that can be involved. You definitely don't want to miss assessment of complex psychomotor function, attention, working memory, executive functioning, learning, memory. For learning and memory, both visual and verbal, because there have been some differences found there. So it's important to include that, as well as visuospatial and verbal functioning. I absolutely encourage people to include a comprehensive battery. Beyond that, I would want to ask lots of questions about access to care, and who are the supports in a person's world, to be able to include those pieces of information for feedback and recommendations.

John Bellone 52:32
One other question that I just thought of. I know this is backtracking a little bit, but...

Monica Rivera Mindt 52:35
It's okay.

John Bellone 52:36
In terms of the cognitive profile or the severity of cognitive deficits, do we know if there's a difference between illicit and licit drugs? Like the prescription Oxycontin versus heroin, in terms of the profile?

Monica Rivera Mindt 52:51
Not that I'm aware of, John, but again, if we're just thinking about the brain, there's really not that much of a difference, right? Because these are opiates that are being converted to opioids in the brain and synapse with those receptors. So I don't know that there's a difference. It's a great question. But I don't know if anybody's done that work. However, again, because the illicit substances are being cut with fentanyl, there might be some differences now in the last several years that might not have been present before, but I just don't know.

John Bellone 53:22
It's a good point.

Ryan Van Patten 53:22

Monica, you had mentioned this earlier when listing potential ways that neuropsychologists can benefit people with opioid use disorder and/or who are on maintenance therapy, one of which would be cognitive inefficiencies and impairments that can impact people's ability to benefit from treatment, right? So be that taking the correct dose of buprenorphine at home, or if it's a more intensive substance abuse treatment program where there's information to learn and remember, to the extent someone has difficulties in those areas they may not benefit from treatment. This is sort of an abstract question, but do you have any general advice for how we might take someone's neuropsych profile and then provide recommendations for them to best benefit from therapy?

Monica Rivera Mindt 54:09

Sure. So I think it depends on what the nature of the cognitive impairments is, of course. So if the issue, for instance, is executive function, we're going to recommend compensatory strategies that would help individuals get more organized in terms of their medications or getting to appointments, right? Those kinds of things. Think if the issue with executive functioning is impulsivity. Now we're going to be concerned about risky behaviors and we might also integrate targeted interventions to minimize engagement in, say, risky sex practices or ongoing injection drug use to at least use safe needles, for instance. So that would be one example.

Another example, again, we know that learning and memory can be impacted. If that's the case, then we might recommend that individuals use cues, alarms, reminders to take their medications, for instance, if they're taking buprenorphine at home. Or reminders to make their appointments, because, as I noted, I'm a big proponent of evidence-based approaches to treating opioid use disorder like medication assisted treatment. But, again, that has to happen within this comprehensive approach that is not just a pharmacological treatment but also behavioral treatments, psychological services, and I certainly hope within a socio-cultural context. So that whatever the recommendation, it's integrated into that person's socio-cultural context and their lived experience so that it can be an effective intervention and effective recommendation. Is that helpful?

Ryan Van Patten 55:46

Yeah. Very much so.

John Bellone 55:47
Yeah. Just to wrap up, any other pearls of wisdom in this area or other recommendations or anything for us?

Monica Rivera Mindt 55:54
So a couple things, I guess. Thank you for asking. If folks are interested in knowing exactly what the United States is doing right now to address this critical public health crisis, I encourage folks to look up the Health and Human Services 5-Point Strategy to deal with the opioid crisis that was implemented in 2017 and continues. That's one place to get some information. The Health and Human Services is advocating for access, for more data, for better ways to address pain, better ways to address overdoses, and certainly more research.

My plea for everyone is that they absolutely remember that opioid use is a chronic condition that is amenable to treatment. Again, as I mentioned, if we think about this in terms of a chronic care condition, we can avoid stigma. I'm also a surfer, so I'm going to give a surfing analogy here. You know, when big waves come, people can wipe out, but they can always ride the next wave. Similarly, people might not always stay engaged in care, but we can always re-engage them in care. Thinking about this in terms of a long-term comprehensive approach, certainly always encouraging frequent and ongoing connection with providers, social support and engagement with those who can be helpful. That's my first point.

I also want to remind folks that medication assisted treatment with opioid agonist treatment is related to improved clinical and cognitive outcomes. So I urge folks to take a harm reduction approach to treating opioid use. For all of those who are neuropsychologists out there to really think about the role that we can take to contribute to helping end this crisis. We can be an important part of the solution if we all just join together and start asking the right questions and get engaged in the process.

John Bellone 57:53
Excellent. Wow.

Ryan Van Patten 57:54
Yeah. Great words of wisdom. Thank you again for your time, Monica. Coming back to NavNeuro a second time. We didn't scare you away the first time. [laughs]

Monica Rivera Mindt 58:03
[laughs] No, you did not.

John Bellone 58:05
I didn't know you were a surfer. Next time you'll have to take a trip out to California and we can...

Monica Rivera Mindt 58:09
Very good. You don't have to ask me twice. [laughs]

Ryan Van Patten 58:11
[laughs]

John Bellone 58:13
All right, Monica. Thanks again. Really appreciate it.

Monica Rivera Mindt 58:16
Wonderful to be with both of you. Thank you so much.

Transition Music 58:18

John Bellone 58:22
Well, that does it for a conversation with Monica. We hope you enjoyed the episode and we wanted to remind you to email us at feedback@navneuro.com if you have questions that you would like to see answered in the book Becoming a Neuropsychologist that we're working on. Thank you so much for listening, and join us next time as we continue to navigate the brain and behavior.

Exit Music 58:41

John Bellone 59:05

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Ryan Van Patten 59:17

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