Week 1 - Neurobiology & Stimulants (8.3.23)

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SUMMARY KEYWORDS

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00:06

Hello and welcome everyone! I'm giving a couple minutes so everybody can get their sound connected.

00:26

Also, in the meantime, for those of you that feel comfortable with it, please feel free to share your video and be on screen. We would love for this session to be as interactive and you know, engaging as possible. Hello, hi, Melinda. Hi, Erin. Welcome in. Hello, Charlotte welcome.

00:53

It looks like we have quite a few folks joining. So I'll just give them a second to get situated and then I'll kick us off by sort of giving you a rundown of how today will work.

01:10

Welcome everyone! As a reminder for those who just joined if you feel comfortable with it, and are able to please feel free to turn on your cameras, we would love to have this session be as engaging and interactive as possible. All right, it sounds like most people are logged in. So just to kick us off. Nice to meet you all. My name is Giulia DeMello and I'm the project manager for the review course and I'm just here to facilitate this meeting. The way we're going to structure things today is we have about 18 practice questions that we'll go over and Dr. Baumann will share his slides and you'll be able to see them and put your answers into the chat. And then he'll go over the correct answer in rationales. But, at any point, if you have additional questions, if you have follow up questions, or even lingering questions from the live course, feel free to raise your hand or to type them into the chat and we can address them as we go. At this point, I'll turn it over to Dr. Baumann to introduce himself, and then we can get started.

02:09

Okay, thanks so much. And also thanks for all the participants. And hopefully today we can be giving you some some help with Practice Test Questions. And so as I already mentioned, what I'm going to do we share my screen and we'll go through the questions one by one. I'll show the question. And then folks can answer. And we'll give you a few minutes to look at the question, read through it and then we'll go over the answer. And as we're going, I guess, so, so is it okay for people to ask questions throughout? Yeah. So they don't really have to be in the chat. I think you could probably just chime in, feel free to chime in if you have questions. That's - we want to keep this as informal as possible. The other thing is if people have questions, please don't be afraid to ask because that's the whole purpose of this so that folks can can get the answers that they're looking for. Okay, share my screen.

03:25

Can people see my screen?

03:28

Not yet. All right. I also have it pulled up if you'd like me to share it. There it goes.

03:42

Can you see it now?

03:43

Yes, but it's not on presenter view. Yeah. Yeah.

03:51

How about now can you see it?

03:58

Yes. How's that look? Perfect. Okay. So we're gonna just jump right in. First question. 26-year-old woman contacts you because she's considered performing an intervention. Now, I have to do something here because I can't see the side of it. Thanks, 30-year-old husband to get him into treatment. He's exhibited bizarre and erratic behavior increasingly during the past year, staying up all night, talking rapidly, acting suspicious, sometimes frankly paranoid. So also experienced bouts of severe depression. She's quite sure that he has had affairs and has gone deeply into debt. She knows that he's used some drugs in the past but does not know what. She thinks he may be using again. The most likely substance here is A alcohol B, heroin. C, cocaine D Lorazepam. So I'll give folks a few minutes to think about this. and the beauty of it here is you're not going to be graded.

05:13
Okay, I'm going to go to the next slide which provides the answer. The correct answer here is C. So

05:24
the correct answer is C. Okay, now what's going on here? Do I not have these?

05:33
I don't have the answers, I guess. Oh, there's no explanation. But did you did you? Did you put the explanations in, Giulia? No, they're not in the slides. They're in the document.

05:42
Okay, that's fine. All right. So the correct answer here is C is cocaine. And so what's happening here is this this person is probably have severe cocaine substance use disorder. And this is what is underlying these these particular symptoms here, especially in the bizarre and erratic behavior, the oscillation between sort of paranoia and depression, these are characteristics of cocaine misuse. Next question. Which of the following drug screening immunoassays is most commonly found to have false-positive results? A amphetamine B benzodiazepine, C cocaine, D cannabinoids.

06:37
And it looks like on the chat, we have some folks putting in their answers and they're both saying A so far.

06:48
Okay, so the correct answer here is amphetamine. And so there's a number of things to talk about here when we consider false-positives on immunoassays. The first one is cross reactivity with other drugs that have the amphetamine type, structural scaffold. Remember, immunoassay is targeting the chemical structure of the molecule. And for example, Wellbutrin - which is actually a cathinone - it has amphetamine nested in its structure. But other folks could think of amphetamine itself, if someone, for example, is taking ADHD medications, right. So so this is not necessarily a false positive, it's actually, it's actually an accurate result. But it's not someone who's taking substances illicitly. And so, we'll get to this in a in a subsequent question. The most rapid delivery of cocaine to the central nervous system occurs with A oral ingestion, B intranasal or insufflation, C intravenous injection, D smoking cocaine base.

08:14
Looks like we have a mix between C and D in the chat.

08:18

Yes, so. So this is a really good example of a very detailed question, because both of these, both of these routes are going to give you very rapid amounts of drug quickly into the brain. But the correct answer here is D. And the reason is, this has to do with the physiology of the systems involved in the delivery of the drug. Now, when you smoke the drug, you get it into the lung epithelium and the lung circulation, which is totally set up for instantaneous delivery of substances into the brain. And so smoking cocaine base is going to put the drug into the brain somewhat faster than intravenous injection. When you inject into the venous system.. When you inject into the venous system, it has to go into a into the heart and then be pumped out into the into the circulation. So even though intravenous injection is rapid, it's not as rapid as smoking. And folks, if you have questions about this, please, please ask.

09:39

On that note, just as a reminder, if you want to unmute yourselves, you're able to and you can ask the question directly or you can throw them into the chat and I am happy to read that out loud. We did get one question that says can you go over that one question one more time. Which one? The previous one? The previous question.

09:56

Okay. So the answer to the previous one Question. That's good. So this is important that you stop me on these because you might not, you might not be fully understanding what's going on here. When you smoke cocaine, the smoke delivers the cocaine directly to the pulmonary vein, which then enters the heart where the blood is pumped directly to the brain. When you give it IV, it has to circulate through the venous system first, get to the heart, then lungs and then be pushed into the brain. Okay, it has to be oxygenated at first. So the path for the cocaine to travel intravenously takes longer than the direct delivery into the pulmonary circulation. I hope that - which is going to go directly to the brain - so, I hope that that answered the question. Did that answer?

10:49

I believe so? They said, "I see" and "thank you." And then the other question that we also got was, "Is this also true for meth and heroin?"

10:58

Yes, yes, absolutely. Yep. This is a route-specific. So that's a that's a good point. So in some way, you can cover several other questions by knowing that this smoked route is the one that actually delivers, in every case, the drug faster to the brain. Next question, according to experimentation with rat models, which of the following substances produces the greatest release of dopamine in the nucleus accumbens with recreational use? So this has to do with dopamine release in the circuits involved in addiction? A is cocaine, B is heroin, C is methamphetamine, D is mescaline. So which of those drugs gives the greatest release of dopamine in the nucleus accumbens?

11:51

So far in the chat, we have a consensus on C.

12:00

Okay. Now, for this one, the answer is methamphetamine. And so sort of the rank order of which drug is giving the most dopamine in the extracellular space, methamphetamine gives you the most. Heroin gives you the next. Sorry, cocaine gives you the next, heroin gives you the next and mescaline doesn't really increase extracellular dopamine because it's a serotonergic drug. And so the reason why methamphetamine gives a greater increase in extracellular dopamine is because of the mechanism of this drug. It actually works as a dopamine releasing agent. It binds to dopamine transporters, it actually goes into the transporter and causes that transporter to work in the reverse direction. So this reverse transport, through the transporter, allows very large elevations and extracellular dopamine, much larger than you would see with a drug like cocaine, which acts at the same site, but just simply sits on the outside and blocks reuptake. Okay, so because Methamphetamine is a releaser of dopamine, you get a larger amount of dopamine released. Again, feel free to chime in or in the chat if anything's unclear. The next question Oh, this is kind of gave it away. cocaine and amphetamine share which of the following neuropharmacological mechanisms? A MAO inhibition, B sodium channel blockade, C disruption of function of neuronal membrane transporters, D blockade of dopamine receptors.

14:01

So far in the chat, we have a mix of D and C.

14:07

Okay. The answer here is disruption of function of neuronal membrane transporters. In the previous question, I explained the difference between the mechanism of action of cocaine and methamphetamine, specifically at the dopamine transporter because this is the membrane transporter that's most implicated in the abuse liability of these stimulant drugs. So, just to, before I move forward, these drugs, stimulants in general, do not directly block dopamine receptors, they don't act at dopamine receptors. They act at transporters. So in some manner of speaking, when you take these substances, you're getting high from your own neurotransmitters. Your own dopamine is being elevated in the extracellular space. So they don't target receptors they actually target neuronal membrane transporters. Cocaine targets the transporter as a uptake blocker or uptake inhibitor. It just blocks the transporter so it can no longer take up dopamine. Whereas, as I mentioned previously, methamphetamine has a more insidious mechanism, it actually goes in through the transporter, and makes the transporter run in reverse to release cellular dopamine out into the extracellular space.

15:41

The primary enzyme that metabolizes cocaine in humans is: A esterase B Cytochrome P450, C superoxide dismutase, D glucuronidase.

superoxide dismutase, D glucuronidase.

16:05

Okay, the answer here is A esterase, esterase. Circulating esterases, such as butyrylcholinesterase, are the principal mechanisms of inactivating, metabolizing cocaine. Cocaine is a phenoltropane that has a linkage that is an ester linkage that's cleaved to inactivate the cocaine.

16:38

Next question, prolonged substance.. substance-induced psychosis is common with chronic use of: A Alprazolam, B methamphetamine, C PCP, D LSD. Which of these substances is associated with prolonged substance-induced psychosis?

17:03

So far we have consensus on B in the chat.

17:12

That's correct. The answer here is B. Chronic amphetamine and methamphetamine use can cause psychotic syndromes and these can persist in many cases. They can persist for quite a long time, even years after after use. Which of the following interventions has been shown to be most effective in the treatment of stimulant use disorders? A Bupropion, B Sertraline, C buprenorphine, D contingency management?

18:09

Okay. We have D in the chat. That's right. So D is the correct answer here. Now, all of these substances mentioned have been used off label in attempting to alleviate the symptoms of stimulant use disorder with varied effectiveness. Some patients respond, but most do not. And it's important to note there is no FDA approved pharmacotherapy for stimulant use disorder. And so things like contingency management, cognitive behavioral therapy, and even group therapy, depending upon the patient will be much more effective. We still don't have a pharmacotherapy that's approved for use. And again, so contingency management. The problem with this particular modality is it's not widely available. It's been shown in a lot of experimental studies that this is very effective, right? If you give someone as an incentive, for example, give them a job and sort of leverage that to to, to to help them to keep drug free. This is a really effective way for keeping people abstinent from use.

19:36

Next question, use of amphetamines is FDA approved for which of the following clinical conditions? A to assist students with concentration while studying, a a B as an aphrodisiac, C to treat attention deficit disorder in children, D to relieve depression. Which one of those is a, an FDA approved

indication for amphetamines?

20:08
So far we have consensus on C in the chat.

20:12
Yes. Hopefully nobody picked A. Yes. Yes. Okay. So this is by far and away, at least in the United States, this is the primary indication for amphetamine, Adderall, mixed amphetamine salts. It's noteworthy that Amphetamine is also approved for the treatment of sleep disorders such as narcolepsy. It's used off label for for appetite suppression, but I believe that it's also approved for a binge eating disorder. So but the vast majority of amphetamine prescriptions are for ADHD.

21:04
Next question. The husband and 16-year-old daughter of a 42-year-old woman appear in your office concerned about mom's behavioral change over the past several months. Particularly mentioned symptoms are restlessness, sleeplessness, grandiosity, suspiciousness, irritability, along with increasing financial problems. Most likely diagnosis is:

21:35
So far, we have consensus on A on the chat. Yeah.

21:41
Yes, so the answer here is a and the symptoms are, you know, somewhat overlapping with the previous patient that we saw earlier the the male patient, we see a lot of the same sort of overlapping kinds of symptomatology here. Yeah.

22:11
See, this is seen as one of the four Yeah, I don't know if we saw this one before. Here's another. Here's another patient one. 26-year-old woman contacts you because she's considering performing an intervention with a 30-year-old husband to get him into treatment. He's exhibited bizarre and erratic behavior increasingly during the past year. Staying up all night, talking rapidly, acting suspicious, and paranoid. Also experienced bouts of severe depression. Again, we've heard these descriptions before. She's quite sure that he's had affairs and has gone deeply into debt. She knows he has used substances in the past but does not know what substances. She thinks he may be using again, and suspects cocaine use. Patient agrees to go to an emergency room. The best initial diagnostic tests would be an MRI, an EEG, a urine drug screen, or a hair sample test for drug use? Which of those is the best answer?

23:15

I'm seeing lots of C's coming through the chat. And then I also have a follow up question whenever we're ready.

23:21

Yeah, yep. So this is the correct answer. The correct answer is C. The quickest way to tell if someone is on a stimulants - is currently involved with stimulant misuse - is to get a drug screen. And this also is a way to rule out any endogenous type of of psychotic disorder or perhaps bipolar disorder with psychotic over- overtones. So the best way here is to use a drug screen to rule out current drug use, either rule in or rule out, right, either confirm or rule out drug use. Cocaine in particular is detectable through urine screen for two to three days. Now, one of the things want to mention about that the cocaine urinalysis tests, this is related to a previous question, in fact, really don't look at cocaine in urine. We look at benzoylecgonine. That is the product of cocaine that's once the ester has cleaved it. So you're actually looking at a cocaine metabolite. That's a long lasting metabolite. When you do a cocaine drug screen, that's just what's so. Was there - Was there another question?

24:37

Yes. So the first one was actually relating to the last question that we went over, talking about the irritability and restlessness. So Joseph asked the irritability and restlessness wouldn't be months for ethanol. Is that correct? So essentially parceling out what substance we were referring to.

24:59

So what do we go - Is it the previous question that was referring to?

25:02

Yes. previous question. Yeah. Okay. So

25:09

yes. Okay. So, irritability and restlessness by themselves would be much harder to diagnose. Grandiosity and suspiciousness, though, these are aspects of the symptoms here that you would not, you wouldn't see these with with alcohol withdrawal. You wouldn't see these. You, you very well could see restlessness and irritability. Right. So you could see restlessness and irritability, with withdrawal from a number of different substances. But this issue of grandiosity and suspiciousness and paranoia, this is this is exclusively for the stimulants. So one or two of these symptoms alone isn't isn't enough to make sort of the the proper guess as to what's going on here. But if you have a number of these,

26:06

26:06

and particularly the grandiosity and suspiciousness. And then - I hope that helps to answer that question.

26:14

And and then a little bit more of clarification to the question was, alcohol it is just asking if alcohol would cause more transient rather than months for the symptoms?

26:26

Well, that's that's a good question. Okay. So I'm not an expert on alcohol and alcohol withdrawal. The other thing about alcohol withdrawal is it has more physical, I think it has I think it has more physical, rather than solely behavioral symptoms, that you would see. Right? So alcohol withdrawal would be would be would be different. Because you don't have grandiosity and suspiciousness. And you also would have more physical or physical problems, depending upon how long the withdrawal is, right? You would get tremors and things like that you'd get tremors and you would have physical changes that you don't see with cocaine withdrawal, or cocaine use. I hope that answers the question.

27:14

I believe so. And then we had another question, which was why does meth cause such prolonged psychosis?

27:21

Ah, that's a really great question. I don't think that I'm not sure whether or not that's known. Now, one thing I will mention about methamphetamine, and I've alluded to this already, is that its mechanism of action, even though it affects dopamine transporters, as cocaine does, it causes these tremendous increases in extracellular dopamine. So you get hyperdopaminergic signaling, like this is supraphysiological. This is the kind of dopamine signaling the brain is never- would never see under normal circumstances. And so the idea here is, is that if you have this hyperdopaminergic signaling for so long, that you could have irreversible changes in circuitry in the brain. That's one possibility. Another issue with methamphetamine because of its mechanism, it causes frank dopaminergic neurotoxicity. Unlike cocaine, which sits on the outside of cells, cocaine sits on the dopamine transporter on the outside of cells. Methamphetamine goes in through the dopamine transporter and is actually trapped inside of dopamine neurons. And in both animal models, and in humans, If this occurs, to a high degree, it can cause frank dopaminergic neurotoxicity. You have death of nerve terminals. And so it's possible that this, these are the two things that I just mentioned, are the underpinnings of this long term of psychosis. But I don't think that we really know the precise underpinnings, we certainly know how methamphetamine works acutely, and we can infer things from that, i.e. toxicity of dopamine cells, and chronic hyperdopaminergic signaling that that irreversibly changes brain function. These would be two hypotheses about why this would happen. The other thing that's important to note that the this issue with the persistent psychotic episodes with methamphetamine, a lot of times these are triggered. So the person isn't psychotic all the time necessarily, right. But for example, stressful events could trigger a psychotic episode. Use of

methamphetamine at doses that in prior use did not cause psychotic episodes now causes psychotic episodes, i.e. behavioral sensitization. So this this is well established with with methamphetamine, right? So rather than having tolerance to these psychotic effects, you actually get sensitization, people become more sensitive to the drug after chronic bins use. And so even low doses can cause frank psychotic episodes. I didn't really answer the question. I just gave you some factoids. We don't I don't really think it's known exactly how that occurs. Oops. Okay. Other questions?

30:40

We got a comment first. This is great info. So I think the factoids were well-received. And then the other question was, just if you could go over again, how cocaine and meth differ on the dopamine receptor, or act differently.

30:59

Okay. Yeah. So I don't really have a good picture to show you. So the way the way that all stimulants work - we're focusing on cocaine and methamphetamine here, but actually therapeutically relevant stimulants like ADHD, ADHD medications like Ritalin, all these stimulants work by acting at monoamine transporter proteins. These are transporters that their normal job is to take up transmitters like dopamine, norepinephrine, serotonin. I'm focusing on dopamine because dopamine is the one that's involved in the addictive properties of these substances. And we are here talking about addiction, so... the way that cocaine acts at the dopamine transporter that binds to that transporter protein. Now, just to back up for a second, this protein, because it's a transport protein, it has a permeation port. And normally what happens is dopamine, right, your endogenous transmitter molecule, dopamine will bind to that transporter at the extracellular side. It will bind to the transporter and then be shuttled in through the transporter permeation port to the inside. And then that dopamine gets put in vesicles inside of the nerve terminal. Okay, this is the basic sort of biology about how neurons work, right? These neurotransmitters are taken up by that transporter, and then put into vesicles. And recycled for use. Now. That's the normal scenario. Cocaine will bind to the outside of that protein. And it will block that protein from taking up dopamine. I always use the analogy of a vacuum cleaner. The dopamine transporters like a little vacuum cleaner that vacuums up dopamine. What happens if you get a sock stuck in your vacuum cleaner? It can't suck up anything anymore, right? So cocaine acts like that sock, it gets on the dopamine transporter covers the permeation ports so that dopamine can no longer go inside. So what's going to happen? Now you have elevations of extracellular dopamine because that transporter protein can't do its normal job. So that's the simplest mechanism. That's cocaine, it just simply binds to the transport and blocks uptake of transmitters. Methamphetamine does the exact same thing as cocaine, except it actually goes in through the permeation pore of the transporter to the inside of the cell. And once it gets inside the cell, it disrupts vesicles. And so you have a tremendous amount of dopamine now floating around inside the cell. And then that comes out through the transporter protein. Because another thing that methamphetamine does is it causes reverse transport. If you could remember just one sort of soundbite about how methamphetamine works. It's a releaser of monoamine transmitters and it releases by reversing the transporter's normal direction of flux. Okay? The Transporter runs in reverse. And so now in the presence of methamphetamine, it causes dopamine to leak out and this is why you can get such huge increases in extracellular dopamine with methamphetamine. Because it runs the transporter in reverse, which is quite different than cocaine which just passively sits on that port and blocks. Okay? I hope that that that is clear. So, suffice to say the mechanism of methamphetamine is much more complex. And there's so many spin offs to that complex mechanism

because methamphetamine enters cells through the transporter. It actually goes into the, into the cell through the transporter. And that's responsible for some of the toxicity in psychotic- psychotic episodes that we discussed previously- that I mentioned previously. Cocaine doesn't do that. It just sits passively on the outside of the of the transporter. It doesn't go into the cells and doesn't cause intracellular damage into nerve cells. I hope that's, that's clear, cleared things up. Cocaine is an uptake, inhibitor or uptake blocker. Methamphetamine is a releaser is a dopamine release are okay. They both bind to the same sites, but their underlying mechanisms are different.

36:06

I hope I didn't confuse people more. Okay, next question. Acute renal failure associated with cocaine use has been reported one mechanism leading to acute renal failure in patients who use cocaine is: A renal papillary necrosis, direct toxic drug effects on renal tubules, renal artery spasm leading to ischemia, ischemia, and rhabdomyolysis with myo-globin-uria, myoglobinuria. Which one of these is the correct answer? Now we're getting down in the weeds on renal function here. The correct answer is Rhabdo. Now, it's been shown that cocaine doesn't really have direct toxic effects on the kidney though, what it does is it causes muscle protein breakdown, and you have increases in muscle protein in the circulation. And this gets them into- it can clog kidney tubules, for example. So this is the chief mechanism for renal failure in cocaine use. By the way, this is associated with high-dose cocaine use. High-dose, high-dose binge use of cocaine over a long period. Which of the following disorders is most often misdiagnosed as an acute schizophrenic disorder paranoid type? A amphetamine delusional disorder, Bipolar Disorder, bromide delirium, Hypro- hyperthyroidism? Which one of those answers is correct?

38:09

You've seen this quite a bit already here. The correct answer here is amphetamine delusional disorder. Now this is... this question here is a complicated question because you can sometimes get bipolar disorder with psychotic overtones where we're bipolar patients have psychosis. So, amphetamines induce symptoms of psychosis. It's very similar to acute schizophrenia. Since the presenting mood state of bipolar disorder is most commonly depression, it's not going to be the likely case, right? People that are- that have Bipolar patients with bipolar disorder don't typically come to the doctor when they're manic in the manic phase of their disease. They come when they're depressed. Delirium states, these are characterized by clouded sensorium, right? So this, they're not associated with paranoia. Right? So delirium is one thing, right? To be delirious usually doesn't include a paranoia. And finally, withdrawal from sedative hypnotics is not usually mistaken is psychotic disorder, because delusions again, they're not- you don't get paranoid delusions with this kind of syndrome. It's more associated with hyperreflexia and tremor.

39:40

We have a question in the chat. It says "Do you have any recommendations on treating meth psychosis?"

39:48

Ah, yeah, I think there's probably, there's probably two ways one is to give antipsychotic medications

Ah, yeah, I think there's probably, there's probably two ways one is to give antipsychotic medications but sometimes people worry about the malignant hyperthermia, which I think the risk of that is overblown. But antipsychotic medications would work with benzos. For example, when people present with these bath salts, years back when there were people were coming into emergency rooms with, you know, agitation and paranoia, they basically would give them benzos, they put them in, they put them in the pscych - they go to the psych ER, and they would get, they would get benzos until the effects of the drugs wore off. So either one of those will work, you know, to treat the symptoms, basically, you treat symptoms, one is antipsychotic medications, but in many cases, people that are experienced and this is, especially if they're experiencing it from drugs, until those drugs wear off, you might have people that are super aggressive and even combative. And so they're actually a danger to to the health professionals in the hospital or in the ER, where these folks are being treated. And so giving them benzodiazepines is is, is probably the best bet.

41:04

Then we have another question, which says, "Do you ever see prolonged paranoia with cocaine?"

41:11

That's a great question. That's a great question. You know, full disclosure, I don't treat patients, right? I am a PhD scientist who works at the National Institute of Drug Abuse, but I'm pretty conversant in the literature. And so you do see acute psychotic episodes with cocaine, but they usually wear off when the drug wears off. And so you don't have sort of this prolonged, long-term psychotic situation, once a person is off of cocaine. In fact, what happens when a person who has been using cocaine they was psychotic, acutely.. What happens to someone like that, who doesn't take cocaine anymore? They get serious depression, right? They get and anhedonia, the inability to experience pleasure, and a very sort of major depressive symptomatology. And this, this type of symptom actually drives many patients back to reuse cocaine because the crash that depression afterwards is so severe for them. So no, cocaine is not typically associated with with this prolonged psychosis. The other thing is important to mention even acutely, right? One of the things I talk about in my lecture, is that, you know, you can compare and contrast, cocaine and methamphetamine because they're both prototypical stimulants, but there's things about them that are quite different. Cocaine because of circulating esterases and because it is a phenoltropane with an ester linkage, it is metabolized very fast. So effects of the drug war off pretty quickly. And its mechanism of action to you know, is really not conducive to sustained effects. Methamphetamine, on the other hand, is metabolized very slowly in the principal metabolism of methamphetamines is the alkylation, which gives you amphetamine. So methamphetamine could actually be thought of as a pro-drug, because its major metabolite is amphetamine itself. And so it has a very prolonged action. The other thing, as I mentioned, its mechanism is quite different. It gets internalized in cells, in many cases it can, it gets trapped in cells. And so these are probably the reasons why methamphetamine has this sort of longer term, psychotic type of effect that you don't see with with cocaine.

43:54

Next question, which drug is most commonly associated with acute myocardial infarctions with active use, and people between 18 and 45 years of age? A, psilocybin, B, heroin, C, cocaine, D alcohol. Which one of these drugs is associated with myocardial function? In people between 18 and 45 years of age, which by the way, this would constitute young people. And the answer here is cocaine.

Cocaine, it's a common drug of abuse associated with myocardial infarction following acute high-dose use, even in young people. In fact, young people that have had heart attacks, this is one thing you must really be suspicious of. It's a stimulant, because, because it increases the release of monoamine trans- transmitters, specifically in this case, we've been talking about dopamine for neural, sort of the neural component right the neuro component of cocaine's adverse effects. But here we're talking about cardiovascular adverse effects of cocaine. These are mediated by the noradrenergic system, norepinephrine and epinephrine. And so these elevations and norepinephrine they have, they have direct effects on the heart. But they also have direct effects on vasoconstriction. Right vasoconstriction you can think about the old analogy of the hose with water going through it, what happens if you step on that hose and increase the pressure within that hose? Well, now you've seriously compromised heart function, because the heart has to push the blood against high blood pressure, right? And so anyone who, who who has any kind of sort of vulnerability to heart dysfunction, this could trigger a heart attack. So cocaine causes vasoconstriction. Another thing it does, it causes platelets to adhere together. And so this sort of sticky platelet syndrome can also not only cause, you know, failing of coronary arteries, but also cerebral arteries, which can give rise to strokes as well. So if you see in patients, young patients, especially you see, a, an unusual heart or stroke problems, you know, one of the things to look for is, in particular cocaine, cocaine misuse. "Bath salts", commonly consists of synthetic analogues of: now, I had bath salts in quote, quotes there, and this is refers to some products that were sold, I'd say maybe 10 years ago, these have faded away, although they're still around in the clandestine drug markets. So they're called bath salts as a way of sort of skirting regulatory control. They have nothing to do with bath salts, they are actually powerful psychotropic drugs and so are they: A LSD, B cathinones, C methamphetamine, D Ecstasy. So what are bath salts? psychoactive vessels. Okay, the correct answer here is B cathinones. Now, people may not be familiar with cathinones. There's one sort of a simple way to think about what these are. Cathinone has the same exact chemical structure as amphetamine. The only difference is in its structure, it has a moiety called- a chemicals moiety, a chemical group called a beta keto group, a double bonded oxygen group. And so cathinones, you can think of these as beta keto amphetamines, right? Because they have this added beta keto group in their chemical structure. But suffice it to say they have effects that are essentially identical to those of other amphetamine-type stimulants.

48:22

Next question, how would a medical review officer, an MRO, report to an employer a drug test result positive for an amphetamine when the MRO is presented with evidence that the employee has legitimate amphetamine prescription for a bonafide medical condition? Now, we touched upon this once before when we talked about false-positives. This wouldn't be a false positive, this is legitimate positive, because the person has amphetamine in their system, but the question here is what what the Medical Review Officer do in this in this case? A would they report a positive urine, B a negative urine, C invalid or D cancelled. This is a very complex question.

49:16

So far we have a mix of A and B.

49:20

mix of A and B, right? Okay. Correct the answer here is B negative and so this requires this requires

some some detailed explanation. So regulation is for MRO vary. They vary based upon the setting and the governing authorities under which this testing occurs. But a positive lab test is usually followed up by the MRO team with the employee to determine whether or not the test can be explained by documented legitimate prescription medications. If so, the MRO protects the medical information of the employee and reports the negative test to the employer okay? So in this case, the MRO is obligated to protect the fact that this person is taking a medication and list this positive test as a negative. Invalid and cancelled tests are produced by some failure of the collection or testing procedures that are not assumed to be due to intentional employee efforts to thwart the process, right? So for example, a substituted sample indicates an employee somehow replaced their own sample with a bogus sample, i.e. they got their brother or their sister or their friend to to to hand in the urine sample, for example. And so in this case, it's quite different, like invalid or cancelled samples differ. Here, we're talking specifically about someone that has a bonafide indication. They have a positive amphetamine, but this is probably because they're on Adderall or some other medication and so the MRO is obliged to list this as a negative to protect this person's medical information. I hope that's clear. Intravenous mixture of heroin and cocaine is frequently called: A ludes, B loads, C crank, D Speedball. Which of those is correct? Ludes, loads, crank, or Speedball.

51:36

Correct answer here is a speedball. Ludes are the street name for quaaludes. Crank, is the street name for methamphetamine, specially internasal. Snorted methamphetamine hydrochloride is often called crank. And Speedball specifically refers to the use of cocaine plus heroin. Something called a superspeedball is gaining popularity, and that's methamphetamine plus fentanyl. And so there are users that prefer the mixture of an opioid with a stimulant. And this is becoming more and more common, actually. Sadly, because it really complicates treatment.

52:27

Dr. Baumann, we did get a follow up question to the previous question with the MRO. Yes. So the question is, "if the MRO had the information about the employee's meds ahead of time, they should not order an amphetamine test. Is that correct?"

52:44

Yes, now I can't speak. I can't speak for every MRO, every organization, but yes, if they have the information ahead of time, then they- I mean, they still could they still could order. I mean, they still, you know, if you if you work somewhere where you have mandatory checks, right. A lot of places require they have mandatory drug testing, right? You're still gonna get tested just like everybody else. The thing is, if the MRO has the information, they'll know that a positive Amphetamine is due to do an amphetamine-type stimulant being a legitimate prescribed medication. Yes. I think this this, this one here is probably- this question here would be an example of a situation where that wasn't known to the review officer. But yeah, you raised a good point. In many cases, they would already know this. And if they didn't know that, they would after the first time that a person got a positive amphetamine. Next question, which of the following areas of the brain has been most closely linked with both psychostimulant and opioid reinforcement and drug seeking behavior in general? A the temporal lobe, B the nucleus accumbens, C a the anterior cingulate D, the brainstem. Which of these areas has been closely linked with drug reinforcement and drug seeking behavior? The correct

answer here is the nucleus accumbens. Preclinical studies in animals shown that lesions of the nucleus accumbens will disrupt drug-seeking behavior all together. Similarly, if you locally microinject antagonists into receptor antagonists in the nucleus accumbens, you can, for example, dopamine receptor antagonists in the nucleus accumbens, you can block self-administration behavior as well. So, certainly, there's a really large amount of preclinical evidence in animal models that the nucleus accumbens is sort of pivotal node in the, in the reinforcement in drug-seeking behavior. Well, we've come to the end of our wonderful journey. Questions?

55:30

It looks like we have about five minutes left. So I encourage if you do have questions, if you want to unmute yourself and ask them, there might have been a couple that I missed. I was trying to follow along.

55:55

There was a question in the chat that said "with treating cocaine with SSRI or SNRI while" I think it's "while patient is still using, would that help with the anhedonia and depression?"

56:09

You know, that's, that's, that's a great question, you know? And, you know, I would say, Yeah, that's probably fine. I think that that's, that's okay. Yes, if you believe that the you know, if you're, if you're if you believe that the patient is a relapsing because of the depression that's induced by the withdrawal syndrome. Now, one thing that's important to note is a lot of times, stimulant withdrawal in general, it's not, most of the time, it's really not severe enough for it's not like opioid withdrawal. You don't have physical manifestations and things like that, or opioid withdrawal, benzo withdrawal and alcohol withdrawal you have, you can have frank physical symptoms that are quite dangerous, that can be quite dangerous. But you don't really see those types of physical withdrawal symptoms with stimulants. Nevertheless, sort of the anhedonia and depression that follows a stimulant binge can be very uncomfortable for for certain patients. And if this seems to be driving continued use, I think, you know, treating that is, you know, it seems like a logical, logical end. Now, one of the things that I want to mention here is that there are no FDA approved medications to treat the stimulant use disorders. However, there are a lot of different substances that have been tested, and they're being used by certain physicians off the off label. And so, the newest data, the newest data, suggests that combination of Wellbutrin, that is Bupropion plus naltrexone - bupropion plus naltrexone - has shown some has shown some success or efficacy in treating methamphetamine use. And hopefully, you know, we'll get more data on that topic to, to to show that this could be used, and maybe could get FDA approval. In a similar manner, I think phentermine and Topiramate have been used for cocaine use. And so this, interestingly, is combination of phentermine and Topiramate have been used as an appetite suppressant, have been used effectively for treating overeating. And so there are some commonalities with with with the circuitry that's involved with, you know, food consumption and drug consumption. So that's the idea that you could use an appetite suppressant approach. And this has shown some efficacy for treating cocaine dependence. In general, though, the clinical trials that have tested medications, they, they don't show great results. And you know, there are a lot of reasons why that is. One is a lot of times patients are not compliant. They don't even take the medicine. Another one is the way that clinical trials are arranged to test medication efficacy for substance use disorders,

if you just use on and off urine, whether someone's use drugs or not, right, this doesn't necessarily tell you without quantitative urine assessments, you don't know whether patients reduce their drug use, for example, someone could cut their cocaine use by 50%. And, you know, in some ways, that's a win. But if you're not using quantitative urines, you'd never know have that. So some of this is related to the way that trials are run. Just to come all the way back, though, to the to the beginning of this little blurb I'm talking about here, there isn't an FDA approved medication for stimulant use disorder. But there are substances that are used off label. And it's way beyond the scope of this, of this forum to talk about all those when we get in really get into the weeds because a lot of different substances have been tested for stimulant use disorder. And it failed. You know, they failed to be efficacious. But as I mentioned, they failed to be efficacious. In some way, the clinical trials weren't really the best, you know, they weren't, they could be run better, I think the ones that are being run now by the Clinical Trials Network, here at NIDA, for example, they're guaranteeing, you know, they're verifying rather, they're verifying medication compliance with, you know, riboflavin in the pills so that they can see it in urine, for example. And they are doing quantitative urine assessment. So they can actually tell whether someone actually decreased their use rather than just on and off. So it's hope that in the future, we will come up with some medication that can be helpful for this disorder.

1:01:22

Thank you, Dr. Baumann. And I know we're right at time, so I want to be considerate of it. We do have a couple more questions if you want to address them, or we can. Right. So the first question was just "what is the best treatment for cocaine use?"

1:01:37

Yeah, okay. So because as I mentioned, there's no FDA approved medication, so psychosocial treatments are the best. You got cognitive behavioral therapy, you have the contingency management, which we mentioned in one of our questions, which is quite good, at least the experimental settings, and then, you know, group therapies like, you know, 12-Step. And so, it's up to the physician to decide what's best for their patient, for example, CBT. So cognitive behavioral therapy, this requires, you know, this requires some work on the part of the patient. And in some cases, the executive function of a patient could be such that cognitive behavioral therapy just isn't going to work for them very well. Contingency management, I mean, if you can find contingency management, this, this does work, where if I don't know if maybe maybe physicians have ways of doing this, of sort of figuring out how to implement this in their practice, I would be super interested to know how that works. We have a gentleman here we have a scientist here at Hopkins, across the way across the street from me, I'm at NIDA. But he's over here at Hopkins, Ken Silverman, and he's actually created, He's created a company where he hires people who have substance use problems. And they have a job doing data entry. So he gives people jobs and the way he keeps them drug free is they don't work if they have a dirty urine. And it's remarkable. It's remarkable the incentive for having a job, having income, his success rate in keeping people drug free. Most of these patients are methadone maintained opioid users, but nevertheless, it's an incredible, it's an incredibly effective way of managing substance use disorders, contingency management. And finally, so for some people, things like 12-Step, you know, a sort of a social type of thing works really well, because you know, one of the things that happens with a person who, who has a severe drug problem, whether it be stimulant use disorder, or any other disorder is that they become isolated. And this social isolation, they probably have, they're probably estranged from their families, for example, because of their drug use. And so aligning with a community can be extremely therapeutic and effective. And so

things like you know, narcotics, anonymous, NA, going to meetings, having a sponsor, going through the 12-step program can be really effective for certain patients. And so I don't think there's one size fits all here. But really, psychosocial treatments are the only approach.

1:04:38

Then I'll just do one more question. Just for sake of time. The question was stroke and MI with cocaine. When does it happen? Is it during use or after?

1:04:52

That's a, I don't really have the detail on that. I think it would probably be- I don't think it would be long after use, for example, it wouldn't happen three days later, you know, I think this is something that's probably going to happen, you know, close to- close to drug use, you know, you know, while the effect the acute effects of drugs are going on. Now, with that said, this is a good question, because, you know, I don't know the answer to that. I think it would be probably within proximity with drug use. But I have to admit, I don't know the answer to that. I don't know the answer. I mean, intuitively, I think it would have probably happened when the person was under the influence of the drug. Drug concentrations are high and these effects that are happening on the cardiovascular system, i.e., platelet aggregation, and vasoconstriction are actively happening. And so when the drug wears off, you don't have cocaine induced vasoconstriction. Right? So again, I'm not completely sure because I'm not a cardiovascular expert. But I think this would probably be during use, or shortly thereafter. Not during withdrawal, for example.

1:06:20

Thank you. For sake of time, I think this is all the time that we have for today. But thank you so much, Dr. Baumann, and thank you to everyone who attended and stuck it out and submitted questions. We appreciate it and hope that it was helpful. Do you want to share any closing thoughts, Dr. Baumann?

1:06:37

I just want to say thanks for coming. I hope that that this session was helpful. And, and I wish you all the best of luck in your careers and in your future endeavors. I hope this was helpful for you.

1:06:51

All right. Thank you, everyone. We'll see you next week.