Week 4 - Pharmacology & Toxicology

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00:07

Looks like everybody has connected to audio. So I'll go ahead and start us off. Hello, and welcome. Good morning. This is week four of our office hours. And today we're going to be covering Pharmacology and Toxicology. With us today we have Dr. Lewis Nelson, who presented on this topic during our course. And we have some questions as you already know, prepared. At any point, if you have additional questions, please feel free to either type them into the chat or to just unmute yourself and chime in. We would love to answer as many questions as we can. And yes, this is also being recorded. So you can always find this recording in the eLearning Center afterwards. So at this point, I'll turn it over to Dr. Nelson, I'll send to introduce yourself and then we can get started.

00:48

Great. Yep. Thanks. Hi, everybody. I'm Lewis Nelson. You can see I'm from Rutgers in Newark, you can see my job description there. And the topic is pharmacology toxicology. And I obviously gave this talk at the at the session. And hopefully people came here prepared to think about some of these issues. Some of the the information I'll cover today actually wasn't specifically discussed at the meeting. And if there are questions, I'm clearly happy to answer any of them as we go along. My one problem, if I can call it that is that for whatever reason, I can't see the chat on my computer. It seems to be a new feature zoom added to my computer only. So what we'll do is Giulia will, will let me know if anybody chats anything in. I think that's the current plan. Alternatively, and I'm very happy if you just want to open up your mic and say something, I think that's just as good. We don't have a huge group. At least we don't yet. So it should be manageable. If we want to do it that way.

01:51

That's okay. We'll get going. Okay, so what we'll do, I guess you're going to, I guess, Giulia, we said they chat in their answers. I won't see them. So I don't know if they're going to if they're going to have questions based on the answers. But you can read this probably, it's a long question. So just maybe just read it yourself, rather than me read it out to you because you could read this and I could speak.

02:18

If you don't mind, reading it aloud for the recording. It won't be...

02:23

A 32 year old male patient in recovery from an alcohol use disorder for the past six months presents in your office for routine follow up. He's been attending a-12 step program meeting on meetings on a regular basis and has been seeing a drug and alcohol counselor. His counselor suggested disulfuram, brand name Antabuse as a potential treatment adjunct. And the question is, despite the stem, how does disulfiram work?

02:49

And the options are that it inhibits the metabolism of acetaldehyde is a- B as it inhibits the conversion of ethanol to acetaldehyde. C inhibits the elimination of ethanol via urine. And D inhibits the microsomal- the MEOS the microsomal ethanol oxidizing system, which is one of the which is cytochrome 2E1.

03:13

Right now we have some B's and A's coming through the chat.

03:16

B's and A's are good. And that is actually always tricky. And I think that's good. So it's a good thing to talk about. I'll move on to the answer. And now it's important because it is this- we did talk about a little bit of meaning, although I didn't specifically talk about the disulfiram's therapeutic. But the way the way alcohol, ethanol is metabolized is it goes from ethanol to acetaldehyde. And that is done by alcohol dehydrogenase- ADH. The the medication that inhibits that enzyme is fomepizole and that's the enzyme- that's the antidote that we use for toxic alcohol poisoning.

03:59

Right because those could still be toxic intermediate just like acetaldehyde would be. Acetaldehyde's very short lived in the body, although it is the it is the component of alcohol use that we get concerned about causing aging and cancer because it is it is fairly reactive and toxic. Normally it's metabolized away very quickly by aldehyde dehydrogenase- LDH. That is the enzyme that's inhibited by disulfiram. And so essentially what happens is the acetaldehyde builds up in the blood producing many of the acute effects associated with acetaldehyde toxicity, which really is nausea, vomiting, dizziness, headache, hypertension, sometimes hypotension, etc. Vomiting is a big one, of course. So when people get put on disulfiram, and they drink, they get quite sick. Vomiting is a big component of that.

04:53

04:55

It's sometimes referred to as deterrence or, or or other therapies- often used in law enforcement models and less commonly used I think in most therapeutic models. Ethanol is eliminated by the urine a little bit and we can measure alcohol in the urine but it's not a big component certainly not anything that disulfiram does. And MEOS is, is really not inhibited by disulfiram, or largely by by most of the medications or drugs we use and it allows alcohol to continue to be metabolized slowly, at least in people who don't have heavy alcohol use histories. But this is the enzyme system, the P450 system that gets induced with heavy alcohol use- ADH, the primary metabolizer of alcohol is not really inducible. But as you know that as you drink more heavily and for a longer period of time, you induce the ability to eliminate alcohol more quickly. We call that the development of pharmacokinetic tolerance where you actually metabolize away alcohol more quickly. And you do that by inducing the P450 system. Good. Any questions? Please just open your mic and ask if you have them. Because I apologize again for the chat. I can't I can't explain it.

06:10

Question two. Why are recently abstinent individuals with severe alcohol use disorder who have a history of chronic daily alcohol consumption, frequently less sensitive to the general depressant effects of barbs- barbiturates than nondrinkers?

06:24

And the answers are: individuals who are alcohol use disorder? I can't read the question it's- I'm blocking... absorb barbiturates poorly in the absence of ethanol; in the absence of ethanol, barbiturates- barbiturates binding to the central nervous system is depressed? C- enzymes responsible for barbiturate hydroxylation are inhibited in individuals with severe alcohol use disorder and D- enzymes responsible for barbiturate hydroxylation are induced in individuals with severe alcohol use disorder.

07:02

So far, we have a D in the chat. Another D. But I'm seeing some hesitation only two answers so far.

07:19

It's a tricky question. It kind of plays back on the prior question The correct answer is D. So absorption has nothing to do with anything here. So that A is kind of a gimme. B in the absence of ethanol, barbiturate binding of CNS depressed... there's there is no relationship between ethanol barbiturate binding in the brain. Barbs bind to the GABA receptor, the GABA, which sometimes called the GABA chloride channel complex, and open up the chloride channel allowing more chloride to come in and hyperpolarizing the neuron by by carrying negative charge into the into the neuron.

07:56

Ethanol works the same way. They don't bind to the same site. So that wouldn't really be a correct answer... regardless. So the real question is C or D? So does does barb hydroxylation increase or

answer....regardless. So the real question is C or D? So does does barb hydroxylation increase or decrease? And obviously, the answer is increase. And then the thing you have to know is that barb hydroxylation occurs through P452E1, right, which is the enzyme that's induced by chronic alcohol use. So to so if you think about it, if you metabolize it away more readily, you are less sensitive. That is a classic example of pharmacokinetic tolerance, meaning the kinetics of the drug are changed, making you more able to tolerate the drug.

08:45

Just to be clear, pharmacodynamic tolerance, which is what we usually think of when we think about tolerance, has to do with the fact that the receptor, the GABA chloride channel complex where the both of these drugs bind, becomes less sensitive to the medications over time. And if you'll remember back to the image I use we there's a change from an alpha one to alpha five subunit that makes the GABA channel the GABA chloride complex, less reactive to the binding of alcohol or barbs or benzos, for that matter, and we sometimes call that cross tolerance. So any of those agents that affect the GABA chloride complex, or GABA, will change the pharmacodynamics- the effects attached- that those drugs have upon binding- of all of the drugs that work through that class. So alcohol causes barb tolerance both through inducing its metabolism and through reducing the effect that occurs when it binds through the pharmacodynamic tolerance model. Questions? Please just open up...

10:01

The next question, well, we did not talk about this. But it's an important concept to know, the combined use of alcohol with cocaine is more toxic than either of those substance used alone, because use of both substances leads to the bio-transformation of each substance into which of the following compounds?

10:17

Now, this is a little bit of "you know it or you don't", it's something you should know. It's kind of an interesting idea. And it's a true statement. And we do know a lot of people mix alcohol and cocaine, so B-E is A, cocaethyelene is B, acetaldehyde is C, and cocaaldehyde is D.

10:40

We have some B's coming through the chat.

10:48

So everybody probably recognizes that benzoylecgonine- B-E- is the metabolite of cocaine and what we measure when we measure cocaine in the urine. We're not measuring cocaine. The only people that measure cocaine are medical examiners. In clinical use, we only measure B-E... cocaethyelene is the right answer. If you looked at the- if you looked at a structure of it, it would literally be the two- the benzoylecgonin linked to some extra hydroxylation called cocaethyelene.

11:18

Acetaldehyde- We've talked about it's the metabolite of ethanol at the first step. And then cocaaldehyde is a make believe compound as far as I know, I don't think it's an intermediary compound. And it's just it's just I don't think it actually exists. So right so cocaethyelene, now, cocaethyelene's main effect on on people seems to be that it causes hypertension, right, in the long term. And that's one of the reasons we get more concerned about the combination of use. It may not be an acute effect, but it's a chronic effect and people are more likely to develop cardiovascular disease. Remember, cocaine causes cardiovascular disease in and of itself. So the combination of the two medications actually leads to the potential for worsening outcomes mostly to cardiovascular toxicity. It's not psychoactive, it's not a psychoactive issue. It's a it's a, it's a cardiovascular issue.

12:15

The next question: a 32 year old man has been in recovery for six months from alcohol use disorder, and regularly attending 12 step meetings. He states he wants to go back to work as a truck driver. But he's concerned about returning to use. You discuss the options for medications to help with recovery maintenance, and the patient expresses interest in disulfiram. The primary mechanism of disulfiram... I guess this is a bit of a repeat question. And that's my bad. But let's do it again, anyway, is which of the following: receptor binding affinity, enzyme induction of enzymes that metabolize alcohol, alcohol dehydrogenase inhibition... I'm sorry- aldehyde dehydrogenase inhibition, or reducing the reinforcing effects of alcohol and dopamine in the brain?

13:00

Hopefully, everybody's learned. That's why repetition is a good thing. And maybe I did that on purpose. And we hopefully have the correct answer. Just to go through it. I mean, there really is no effect on receptor binding affinity, which is a complex concept and nothing about this drug would make you think that. We've talked about enzyme induction of enzymes that metabolize alcohol, which occur but disulfiram doesn't do that. Interestingly, D, there are some effects of disulfiram on dopamine, though, disulfiram is is, you know, might actually reduce dopamine, and some of its precursors and metabolites might actually have an effect on dopamine, but probably nothing that would have any clinical effect whatsoever. So clearly, the answer here is A- is ALDH inhibition.

13:52

Just a quick, rapid-. Sorry, sorry to interrupt, but we had quite a few folks that just joined. So just as a reminder, please, if you have any follow up questions throughout the lecture, feel free to put them into the chat or to unmute yourself and just chime in. As always, it's really helpful to have follow up questions if you are not sure about a question so that everybody else can also hear the explanation more in depth.

14:15

And I said, if- if you've joined in, I've already apologized profusely, but my chat functions not working on my zoom. So just if you have questions, please just open up your mic and ask I'd rather answer

them. I know Giulia's gonna follow the chat for me, but I'd rather just have you asked me directly. The most rapid delivery of cocaine to the central nervous system occurs with: A- oral ingestion, B- intra-nasal inhalation or insufflation... C- IV injection, or D smoking cocaine base?

14:54

Seemed to have a mix of B's and D's in the chat, but are mostly D's

15:01

Mostly B's? D. D. Yeah. We did spend a bit of time talking about this at the at the talk. Obviously oral ingestion is almost never the right answer because it has to get in. You got to eat it. It's got to get absorbed, it's gonna get circulated goes to the liver and there's a lot of first pass hepatic elimination- cocaine's not a great drug orally. Inta-nasal inhalation and insufflation is good. And so it's not it's not a bad answer. The reason... and IV injection is also not a bad answer. B and C, and this is where it gets a little tricky. Both involve the use of cocaine hydrochloride. Right, meaning it's the salt form of cocaine, which means it dissolves in water, which is why you can use it those- by those routes. To inject it into your vein, you have to dilute it in water. To put it in your nose, it has to dissolve in mucosal water in your nose.

15:59

D- smoking cocaine base involves obviously the use of a non-salt version of cocaine, called cocaine base. Back in the day, in the Richard Pryor days remember when he, you know burned himself when he was trying to make freebase, it was very dangerous because it involved trying to extract the the base from from a mixture of cocaine hydrochloride dissolved in water using an organic solvent. And if the organic solvent that was often used was ether, and ether is very flammable. So what happened to Richard Pryor, if you remember is he was trying to do that he spilled over the ether onto a lit flame, and it exploded and he burned himself while he was doing it

16:45

What crack basically has done is it's commercialized or industrialized freebase manufacture. So crack is freebase and crack is smokeable. Whereas powdered cocaine is not because crack is not water soluble, but in exchange for losing water solubility in the freebase form, you gain heat stability, right? If you try to smoke powdered cocaine it would just pyrolyze and turn to ash, whereas because the base form is heat stable, you can heat it up and volatilize it, making it inhal- inhalable.

17:23

Why that's important is both for costs. The lungs are a huge area for absorption, as is the vein so you would say well, IV, you get it all in right away, and smoking you get it on right away also. So why would base be better than injection? The next level thinking is injection is a salt, which means charged. Base is not. And in order to get into the brain, there's no uptake pump of cocaine into the brain, it's a passive diffusion process. And charged things don't diffuse very well. So base- crack

freebase gets in much more quickly, which is why it's both a bit more dangerous, and a bit, quote unquote, better. Right now, as I've always said, there's a lot of politics around that. But if you just go to the pharmacology of it, all other things being equal- smoking bass, freebase or cocaine is, quote, unquote, better at rapid delivery to the brain than injecting the salt. You can't inject. You can't inject base and you can't smoke salt.

18:34

The primary enzyme that metabolizes cocaine in humans is: A- esterase, B-cytochrome P-450. C-superoxide dismutase. D-glucuronidase.

18:50

We did talk about this a little bit in passing, I didn't spend a lot of time in the talk talking about it. We're dealing with answers.

18:57

We have a consensus on A so far.

19:00

Good, well, then everybody's right, because it's esterase. Now, a lot of people call this cholinesterase, which is a perfectly fine term, it's a bit more specific than esterase. Some people call it pseudocholinesterase or plasma cholinesterase. But it is a form of acetylcholinesterase. And remember that cocaine can be deacetylated to form benzoylecgonine. But this cholinesterase is the enzyme that does it.

19:28

It is a super effective enzyme. It's considered to be one of the most rapidly functional enzymes in the body, right? It's used normally to metabolize acetylcholine in your neuromuscular junction and other places. But it happens to be the enzyme that metabolizes cocaine too.

19:47

What people have tried to take advantage of the fact that insecticides, cholinesterase inhibitors can block the metabolism of cocaine and they've actually I'd say it's uncommon, but we've seen these folks who use cholinesterase inhibitors to improve the cocaine effect, meaning it lasts longer, they get higher. It's dangerous because you also get insecticide poisoning, pesticide poison. I remember that sludge, salivation, lacrimation, et cetera for those that think about that stuff.

20:20

20:20

B in our review we talked about there's a whole family of agents... 2E1 we talked about with barbs and alcohol. Superoxide dismutase has to do with has to do with an- antioxidants in the blood. Very important enzyme but not relevant relevant here. And glucuronidase obviously, is what is used in the glucuronidation process. So not relevant to your... questions?

20:47

A while while on maintenance dose of method- of methadone, 80 milligrams per day, a patient intravenously injects the equivalent of 10 milligrams of heroin. The most likely effect will be: A- euphoria and sedation, B- sedation only. C- neither euphoria nor sedation. D- lacrimation piloerection and abdominal cramps.

21:18

I'm seeing some confidence C's coming through the chat.

21:21

Confident C. Good. And just to remind everybody why that is the correct answer. This is sometimes referred to as a blocking effect of methadone. Remember that in in clinical practice... all you need to prevent withdrawal from opioids with methadone is probably 10 or 20 milligrams per day. But we give much higher dose in clinical practice. And that dates back to the 1950s. When you know, methadone was first introduced later on in the 70s, when the use of methadone was sort of codified a bit. It's not, it is it is not a detoxification process any longer as it was initially, but it's a maintenance process.

22:00

And what we do is raise the dose high enough, slowly, of course, so that they don't overdose because you do have to develop that opioid tolerance to get to doses of 80, which are probably lethal to most people who are not heavily opioid using. But it ... what it does is it essentially saturates the mu opioid receptor with methadone, so that when you inject heroin, it just can't get to the receptor- plain old, you know, steric hindrance, it just can't get in to the spot, it has to be ... at 20 milligrams, they'd still be able to get high from their heroin. At 80 milligrams or higher, and many of us go higher in doses and that, just the mass effect of methadone being around prevents the heroin from getting in now.

22:45

Now, some people on the street recognize this, and they just scale back their methadone dose, so they could still use opioids recreationally. A- obviously is the opposite of C. B sort of is as well. D of course, is opiate withdrawal- it's alluding to, to that might be true if this was a buprenorphine question, but it's not true if this were... if this were a... heroin injection. Questions?

23:09

23:09

I think everybody probably knows this. But a 29-year-old man is starting treatment for addiction to multiple substances. He has a history of using heroin, marijuana, alcohol, methamphetamine and cocaine. After five days of abstinence, which of the following substances is most likely to still be detected in urine? A- alcohol, B- cocaine, C- heroin, D- marijuana or cannabis? I think most of us now call it.

23:45

Lots of D's in the chat and then I think a B.

23:51

So it is cannabis. Obviously, a lot of this depends on duration and volume or extent of use. Alcohol is the easy one. I mean, no matter how heavily you drink, and essentially no matter how high your alcohol consumption is, it's gone by the day or just a couple hours. And we know the rate. In an alcoholic naive user, somebody who drinks casually, they probably eliminate alcohol at about 15 milligrams per deciliter per hour. Remember, 80 milligrams per deciliter is the is the quote unquote, legal level or the per se level for driving. So if you think about 80 as the per se level if you drink enough, which is about four drinks in a 70 kilogram man to get to 80 You need to have that 15 milligrams just per hour, and it'll take you probably six hours or so for it to be all gone.

24:47

Cocaine. We're not measuring in the urine. We're measuring benzoylecgonine. Cocaine is gone in moments. It probably only lasts for a half an hour, 40 minutes, maybe an hour, which is why the medical examiner can use it because they find cocaine in somebody who's dead, it means they've used cocaine very recently before they died. But the metabolite lasts for about three days. And it almost doesn't matter how much you use, it doesn't last a lot longer than that there's no bio accumulation of benzoylecgonine. It's very water soluble, and it just gets eliminated.

25:18

Heroin, we don't measure heroin in the urine; either we measure morphine, but still same general idea- by about three days, maybe four or five on the outside it will be gone, because it's not particularly water so- not particularly fat soluble, and it gets eliminated quickly.

25:34

Cannabis on their hand is very fat soluble. So when you use THC, tetrahydrocannabinol you accumulate it in your fat. So if you smoke pot once, and you don't bioaccumulate a lot by three days, it's gone. But if you're a heavy user as this person would be, it would be present for the better part of a month in most of these patients. At very low levels, obviously, over time, but you can usually find it

solidly for two weeks, but in most people, you can still find it a month out. So that's good and bad, depending on you know who you are and why what you're looking for, but it gives us that window into probably the past two weeks to a month's use. Questions?

26:25

Okay, you're currently attending physician for a teaching service, and are rounding with your team on a 34 year old male patient with a severe alcohol use disorder. You discuss the pharmacology of alcohol with the students. Which of the following is correct regarding the pharmacology of ethanol? A- it cannot be metabolized in the liver. B- it's well absorbed in the proximal small intestine, C- has no cross tolerance with benzodiazepines. D- is metabolized at a relatively constant rate of a h- of 100 milligrams absolute ethanol per hour 100 milliliters, I'm sorry, of absolute ethanol per hour.

27:07

We are getting lots of B's in the chat.

27:14

Good- so clearly, we talked earlier about its metabolism, both alcohol dehydrogenase and MEOS or P-450 live in the liver. So clearly, it's metabolized in the liver. It is cross tolerance with benzos. We talked about that, that has to do with the receptor conformational change to the alpha one to alpha four receptor in the in the in the neurons and the development of pharmacodynamic tolerance- that's cross tolerance between all of those. There's not pharmacokinetic tolerance, because they're all different, or at least maybe between the benzos because they're not as much metabolized the way that barbs are. But that's got to do with P-450 expression.

27:59

D- metabolized at a constant rate of 100 mils absolute ethanol per hour. It is metabolized at a constant rate. We like to say 80 milligrams per deciliter per deciliter per hour, I'm sorry, 15 milligrams per deciliter per hour. It's a little tricky to convert that to milligrams- to milliliters of absolute ethanol. But you can do it by knowing them by knowing the molecular weight. But we don't have to go into that at the time... that we have just... right. Remember, the answer is and this is not the correct answer it's 15 milligrams per deciliter, your blood content per hour.

28:33

And then of course B is true. It is well absorbed in the proximal small intestine- it's actually absorbed a little bit in the stomach, as well. And fun fact, I think we talked about this a little bit is that women absorb it better in the stomach through the stomach than men do. Right? Their levels of gastric alcohol dehydrogenase are lower than men's are. So women absorb a smaller, there's only a small amount getting absorbed in the stomach anyway, but of the small amount that's absorbed women

absorb more of a small amount. So it has a small effect. All other things being equal, same size man, same size woman etc. The woman would wind up with a higher blood alcohol levels of the man would. Right because of that ADH.

29:16

Now some people sometimes who have what sometimes quote unquote, called the Asian flush, but it has to do with this almost like a disulfide bond like abnormality in the metabolic system where they absorb alcohol and it gets metabolized to acetaldehyde. And then the acetaldehyde builds up because the aldehyde dehydrogenase enzyme is quote unquote deficient or dysfunctional relative to the to the to the wild type.

29:45

One of the things that they have learned to do is take medications that inhibit absorption that inhibit alcohol dehydrogenase in the in the stomach, right and reduce the amount of alcohol that's that is absorbed through the stomach, reducing the amount I'm sorry, reduce the amount of alcohol metabolism to acetaldehyde by the stomach, therefore getting lower acetaldehyde levels due to this metabolic abnormality, right, so if you know or you you have this quote unquote, and it's called the Asian flush is much more prominent in people of Asian descent. It's a pharmacogenomic effect. Taking a drug like a, like a, an h2 blocker, like, like famotidine or cimetidine will reduce the delivery of acetaldehyde to the aldehyde dehydrogenase.

30:52

Which route of administration is associated with greatest bioavailability? Very generic question, A- IV, B- oral C- rectal, and D- subcutaneous.

31:08

A lot of confidence in A's in the chat.

31:11

Yeah, good. I mean, that's a pretty straightforward question. The only time it would be a little bit questionable would might be when we talked earlier about the pulmonary administration of a certain drug. Because the lung is a good administe- is a good absorptive surface, it's so large. By oral means, you know, we talked about it swallowing, liver, et cetera, et cetera, you know, it doesn't mean it can't have good bioavailability, because bioavailability is total absorption of the drug not rate of absorption. Right. So you can have two, you can have two routes of administration that have the same bioavailability of this, say 100%, but their peak and the duration of effect would be very different because one is very rapidly absorbed, and the other is very slowly absorbed. But it's what sometimes called the area under the curve, the total amount that's absorbed of a drug that's taken. So the IV route, the bioavailability, is considered to be one. Right? Because everything gets in there's no way can't get it.

32:14

Oral a lot of is eliminated by first pass. Rectal has somewhat of a similar process. But there's also a lot of other reasons through you know, getting absorbed through the mucosal cells interaction with feces, etc. And subcutaneous has has a similar problem with the need to pass through the water phase and the lipid phase and then through the vast- into the vasculature- So a lot of it gets either metabolized or lost, essentially. So IV is almost always gonna be the correct answer. Unless inhalation is an option, and even then IV is generally considered to be the best reduc- just remember, don't confuse bioavailability with pharmacokinetics it's one component of pharmacokinetics. But it doesn't describe all pharmaco- pharmaco is absorption, distribution and elimination. Right. Bioavailability is just how much of the drug that's given actually gets in to the circulation.

33:12

The primary reason for failure of phencyclidine as a general anesthetic in humans, is that the patient: A- developed addiction- addiction to the drug. B- developed seizures during the post op period. C- experienced delirium when they emerged from anesthesia and D- experienced prolonged ataxia postoperatively.

33:36

Lots of C's coming into the chat.

33:39

Lots of which? C, C. PCP, phencyclidine, angel dust if you will, is still used in veterinary medicine. And in human medicine, we use its cousin, ketamine. Ketamine has a lot of the same problems that phencyclidine has, but it's just to a much lesser extent.

34:06

So you know, addiction is a complicated concept as everybody on this call knows. Certainly. It's not one that develops from a good dynamic tolerance, you're not going to withdraw from things like phencyclidine but you will crave it. So you will develop that so called psychological dependence, but not physiological dependence. Seizures don't happen. In fact, these drugs, phencyclidine, ketamine, and dextromethorphan, which all fall into the same category are probably better described as anticonvulsants because they inhibit NMDA or the or the glutamate receptor, which is the excitatory neurotransmitter associated with seizures. Except- delirium is exceptionally common, and probably most everybody gets it. We know that and when we I use ketamine in my clinical practice, although it's on shortage now around the country, so it's hard to get but when- when it's available, it's an excellent drug for its indicated purpose, recognizing that people will often have what's sometimes called emergence phenomenon which are, which is delirium upon the drug wearing off, but when it's given at high doses, it's an excellent sedative and, anesthetic agent. But there's that awakening period where they emerge from anesthesia. And they develop this profound delirium.

35:28

When you're using the drug, recreationally, so you're going from sort of normal slowly down, you pass into this quote, unquote, emergence phenomenon from the other direction. Right? So you're not you're not unconscious, waking up, but you're conscious going down, because you've taken it slowly. People sometimes call that a k-hole. Right? That's, that's that terrible feeling that you don't want to have. You feel immobilized, very paranoid, and people often that get to that level of sedation, stop using ketamine. Because it's just so unpleasant. It's not the place you want to be. Of course, at low level use, it's fairly euphorigenic and people like the- well, wrong description. It's really psychoactive, and is often described as dysphorigentic or dysphoric. It produces unpleasant feelings, but when combined with other agents that take the edge off of the unpleasantness, they enjoy that experience.

36:31

Many people don't like ketamine or phencyclidine for that reason, but those that like it like that feeling of teetering on the edge of dysphoria. When people are emerging, when we use ketamine clinically, we take the edge off of the emergence phenomenon by giving them a euphoriant like midazolam or something along those lines to take the edge off of it.

36:50

And they do get ataxic, but there's no such postoperative prolonged ataxia. But ataxia is a problem from all all three of those, which are called the arylcyclohexylamine class of drugs have almost identical effects, and even the kids that use dextromethorphan get the same effect. It tends to be even less potent, inducing those effects than ketamine and than in phencyclidine. So it's not as widely used by clubgoers say as ketamine is, but it's much more easily available than usual drugs. You can buy it in a pharmacy. It's unregulated or schedule five depending on the state you live in.

37:34

Next question... questions about that, by the way? Next, which of the following drug screening immunoassays is most commonly found to have false positive results? Amphetamines-A; B- B-benzodiazepine, C -cocaine, D- cannabinoids?

37:51

We have consensus on A already.

37:54

Good, right. So remember, these are immunoassays. That means there's an antibody that's directed against a common epitope or part of a molecule. It turns out that many many amphetamines share a backbone, which is something called what's called a phenethylamine backbone. It's a phenol group

with a couple of carbons coming off of it. Add to that all different functional groups hydroxyls, carbons, nitrogens and other things.

38:19

You change the amphetamine composition- you get methamphetamine and, and all of that and methylenedioxyamphetamine, MDMA, and all of the other amphetamines but the amphetamine backbone is still the same. Lots of other drugs have that backbone, including cough and cold medications like pseudoephedrine or phenylephrine including beta blockers, right which mimic epinephrine on the receptor, but sort of antagonize it the way naloxone antagonizes an opioid receptor and those will all give you false positive results because the enzyme the antibody cannot differentiate the function only the structure.

39:00

Benzos don't have as much cross reactivity or false positivity. Among non-benzodiazepines, cocaine is the best of them all. Right, because the the antibodies directed against benzoylecgonine and there's nothing really that we know that looks like that. There are clinical false positives with cocaine, meaning people that use cocaine not knowing they use cocaine, such as people drink Coca tea, but the one thing to remember and it's never an answer is that they got they went to the dentist and got some lidocaine because even though cocaine and lidocaine are structurally similar to some extent, we're not looking for cocaine, we're looking for benzoylecgonine which does not share any resemblance. It's a tiny part of the cocaine molecule. And cannabinoids, there are some cross reactivities, mostly with the synthetic cannabinoids, right so called K2 and Spice, which don't go by names that are recognizable. They go by by typically number names or names that are just so hard to pronounce that none of us remember any of them. So we just call them the synthetic cannabinoids. So those there may be some some cross reactivity but not so much with THC and the cannabinoids. There are a couple of synthetic canna- that look like THC and can cross react with that assay. But it's not really a big problem.

40:23

So amphetamines, that word we sometimes use is that the amphetamine assay is promiscuous, and it likes to interact with a lot of other compounds. You can use that analogy however you like.

40:36

A next question questions about that?

40:39

A patient started opioids for chronic pain describes painful stimuli eliciting more pain than they previously did. What does this represent? A- conditioned tolerance, B- hyperalgesia, C- pharmacokinetic tolerance and D- sensitization sorry, I jumped, I touched my mouse. Everbody knew this anyway,

41:01

They all got B on the chat. So we're good, good.

41:05

So conditioned tolerance is really that quote, unquote, learning to handle your alcohol better, right? It's just kind of, you know, when you're when you drink a lot, you sort of learn what it feels like to be drunk or high or this or that, and you sort of learn, it's learned tolerance. And you know, it's a real, it's a real thing. It's not, it's not a pharmacological concept, specifically.

41:26

Pharmacokinetic tolerance, we talked about a little bit, but that is the fact that when you drink alcohol heavily, you go from metabolizing at 15 milligrams, just per hour, because you rev up your MEOS or your P-450 system, and you unam- metabolize it 30 or 40 milligrams per deciliter per hour, right, you rev that system up, right it's and cross tolerance, of course, is part of that were becoming tolerant to alcohol through through MEOS, or P-450 induction, also increases the tolerance to barbiturates, which are metabolized by the same enzyme.

42:03

And then hyperalgesia, of course, is exactly what this describes. I always like to think about hyperalgesia as the other side of the coin, with tolerance, right, so, and pharmacodynamic tolerance. So So with pharmacodynamic tolerance, we think about the fact that the drug that we're taking has less of an effect, as we use it for a long time. And we like to conceptualize that, as the drug is wearing off, its effect is wearing off, we're becoming resistant to the effects of the drug. It's said in a lot of different ways.

42:44

The alternative to that, which makes just as much sense and actually has a lot of scientific foundation is that rather than the effect of the drug wearing off, the pain is getting worse. If you think about homeostasis, your body wants to have a certain amount of pain. Right? It's possible the drug wears off. And that causes the pain to go back to where it was. It's also possible that your body says I'm not having enough pain, I'm going to raise the level of pain that I'm having to maintain homeostasis, or to maintain that level where I want the pain to be. And that's hyperalgesia. This is a well described with all pain medications, but it's particularly well understood with opioids or OIH is opioid induced hyperalgesia. Opioids cause hyperalgesia.

43:31

This is probably, and I've said this for years, the reason we had an opioid epidemic stemming from pain medications. It's the over utilization of pain medicine, opioids in particular, leading to worsening

pain medications. It's the over utilization of pain medicine, opioids in particular, leading to worsening pain. Of course, stopping the opioid does not make the hyperalgesia go away, or certainly not quickly. So you're inducing this increasing degrees of pain that people are interpreting as wearing off of the opioid leading to more opioid use leading towards hyperalgesia. And a bit of a vicious cycle leading to the opioid crisis, at least in some large part. I can't blame it all on that. Or I should say, I can't attribute it all to that. But it is certainly a big part. And I think that's come out a lot. And we know what's happened over the past 30 years that we've been dealing with this issue. Okay, questions? Okay.

44:22

What property of heroin accounts for its enhanced psychoactive effects compared to morphine? Is it charge, the lipophilicity is B molecular weight is C and potency is D.

44:38

We are getting B's in the chat.

44:40

B's... good. So people are remembering a lot or they knew this already. And they're just, they're just impressing me. So you'll remember that heroin's other name is diacetylmorphine. In England, it's called diamorphine. It's used as a pain medicine. We don't use heroin as a pain medicine in the United States. Most countries don't. But it is a perfectly fine pain medication. We use hydromorphone, which has a lot of the similar characteristics of heroin. And it does especially given in IV it does have a lot of the same properties and parts of the country and parts of the world that substitute opioids for heroin like effects, they usually use hydromorphone, right, which we call dilaudid in this country.

45:28

The advantage of adding those two acetyl groups to the morphine molecule is they increase lipophilicity- its lipid solubility. They do increase its molecular weight. But that has nothing to do with anything. It's a true statement. But it's unrelated.

45:43

Its potency is higher. But remember, I always like to remind people, that potency is almost irrelevant in our world because you can always take more. So the potency of heroin is about twice that of morphine.

45:55

So five milligrams of morphine will be the equivalent to two and a half milligrams of heroin. But there's nothing from stopping you from taking more morphine. If that were the issue, but it's not the issue, because you could take more morphine and almost no matter how much morphine you took,

it's not going to get you high because it doesn't get into the brain very well, because it's not very lipophilic. Right? They're both charged. Right? And that's life. And that's just the way the way it is that you can you, you know, if you want it to be water soluble, at least, it's going to have to be in the salt form, which means it's going to become charged when you dissolve it in water. There are base forms of heroin, which are smokeable. Right, and there are base forms of fentanyl that are smokeable. And there are sold forms of heroin that are not smokeable but that are injectable, and there are base forms of fentanyl that are injectable- that's the kind we use in the hospital typically.

46:59

And that's the citrate salt of fentanyl, but this same answer applies to everything. Question?

47:07

Okay, classical hallucinogens decrease the activity of which of the following neurotransmitter systems? A- dopamine, B- serotonin, C- acetylcholine, D- GABA, or gamma-amino-butyric-acid.

47:25

Very confident B's in the chat. Good.

47:30

So there's actually there's, these are complicated, the answer is correct to B. Probably all of them have a role at some level. But the classic classic hallucinogens like LSD is a 5HT2 agonist and 5HT2. 5HT is serotonin, and there's multiple serotonin subtypes. And there's there's sub subtypes. So we think about 5HT2A and 5HT2B and you have 5HT3, which is the antiemetic one, which is what we give people drugs like ondansetron, et cetera.

48:05

Dopamine is active and is the rewarding part of of a, of a hallucinogenic experience. But but clearly, if you say what is LSD bind to, it binds to the serotonin receptor. If you look at LSD, or if you looked at a tryptamine, of which LSD is a type, things like 5...DMT dimethyltryptamine or bufotenine, which is an animal derived hallucinogen from the from the dark... from the Bufo Toad, you would see that they're structurally very similar to serotonin. Right? They have that that two ring structure with a five member attached to a four member sometimes called indole ring, right?

48:53

And they're very similar to serotonin. So that's how you know they bind to the serotonin receptor, but other receptors are active in the hallucinogenic process. But clearly the answer here is that these enzymes, these agents bind to the serotonin receptor and elicit effects at other receptors.

49:13

Doctrine also Nelson, we did get a question from the previous question. So it says just to jump back to the last question, would base forms of heroin and fentanyl also get to the brain faster than IV like the cocaine question?

49:26

Yes, and in part because they are not charged, and in part because the route through which they're administered is more pharmaco- pharmacokinetically beneficial, right? You would not insufflate them. You would inject the- you would inhale them. So if you were to smoke heroin by chasing the dragon, or you would have smoked fentanyl, it would get into that very large lung absorptive surface area and get in more quickly and it would be uncharged in the blood and more readily able to cross the blood brain barrier, which is only permeable to to lipid soluble things.

50:06

Now I tell you what's, what's interesting is, it's not all lipid solubility, there's a, there's a, there's a ratio we looked at, which is sometimes called the octanol/water coefficient. So it's how soluble in octanol, an eight carbon lipid, to water. And if you were only soluble in fat are only soluble in water, you never get into the brain, you need to have an octanol/water coefficient. That's somewhere in the mid range. Most people put that in the 500 to 700 range is great. Because you have to be able to get into the lipid layer of the brain and out of the lipid layer of the brain. If you're too lipid soluble, you won't get out of the lipid layer. And if you're too water soluble you'll never get into the lipid layer. So you need to be right in that sweet spot somewhere to be perfect.

50:58

Now there you can still do it at other at other ratios. But somewhere you want to be in that middle so you have some lipid and some water but but lipids probably the relatively more important issue because most things we take into our bodies are water soluble in general.

51:22

Okay, a patient comes the emergency department because he is hearing colors and smelling sounds. He reports taking an unknown substance at a party several hour- oops, sorry. Okay, wait. My computer's very sensitive I have-

51:37

A patient comes to the emergency room because he's hearing colors and smelling sounds. He reports taking an unknown substance at a party several hours ago. Vital signs show increased pulse rate of 120 blood pressure of 185 over 98. Pupils are six millimeters. The patient is quite agitated and wants

these effects to go away. Which of the following drugs is most likely to be causing these effects? Is it cocaine A B? I'm sorry...

52:01

Amphetamine- A. Cocaine- B. Lysergic acid diethylamide or LSD- C or Khat- D.

52:11

We have consensus on C. C.

52:17

Good. And I think that when you hear about synesthesia, which is that description in quotes, it pretty much points you right to serotonin and right to a classical serotonin agent.

52:32

Amphetamine can produce sometimes what are called hallucinogenic experiences, but we tend we typically describe them more as illusions than hallucinations. It's misperception of existing entities not the creation of entities that are not really there. And this mixing of sensory inputs is very classic as well, for a serotonergic hallucinogen. Amphetamine's much more hallucinogenic. Cocaine, of course, can produce psychiatric hallucinations as can amphetamines from, known as tweaking and things like that. Khat is basically a an amphetamine stimulant that is present in the plant that is, you know, used in cultures that use khat the way we might use coffee, in our culture as much- and like cocaine might be used by some civilizations in South and Central America much more as a daily stimulant. Not so much as a euphor- as a as a substance that's used recreationally much more. I mean, it depends how you define coffee use. I don't think most would say we recreationally use coffee. But it would be along those lines with Khat. But again, it contains an amphetamine like...

53:55

Ah, okay, so we could stop there and see what the timing is like, Giulia, I do have five more minutes. Are there any questions we want to go over before I could try to get through one or two more?

54:10

As a reminder, everybody is able to unmute themselves. So if you do have additional questions, feel free to do so. Yeah.

54:15

That'd be great. Please do.

54:22

I have one question. We use ketamine a lot now in psychiatry for depression and for people with suicidal ideation. And I personally don't use it but a lot of my patients do so I'm just there was one thing that you mentioned about ketamine earlier about it, potentially contributing to depression, but certain doses?

54:48

No, I don't think I said that. I misspoke. I don't think ketamine causes depression. Ket- ketamine. I don't remember what the context was what I would have said that...

55:00

Ketamine is used, as you suggested in treatment models, you know, that are, depending on, you know, the science are effective or not effective. But they, if you had to describe ketamine's effect, that would be more of a psychotomimetic, than it would be something that causes depression. It's short lived. It does cause CNS to oh, I might have said... it's CNS depression, is what I... Yeah, that might have been where the words came from.

55:32

So it definitely does. So we just like with, so we always say, and people are coming after using phencyclidine, and their... or ketamine, for that matter. But it's much more relevant to phencyclidine, because the emergence phenomena so stronger. If somebody comes in using phencyclidine and they're still unconscious, the first thing we do is restrain them. Right, because they're deeply sedated, just like the horses that gets phencyclidine for its procedure. Because we know as they emerge, they're going to get agitated and very difficult to manage. That emergent phenomenon is quite ugly. And people remember this whole idea about, you know, people using phencyclidine and turning over cars and you know, jumping off of buildings, and, you know, they have quote-unquote superhuman strength.

56:13

That's really not, that's not really what happens, of course, but they are insensate and unable to differentiate pain, because they are anesthetized, essentially. So you would try to lift the car and stop because you would hurt as your, you know, your muscles would be ripping out of their insertions. These folks don't feel that. That's why they hit their head against the wall for 100 times and crack their skull, whereas others can't. But we recognize that and we know that we should restrain them immediately and sedate them. Right? So that's the CNS depression I'm referring to.

56:50

Okay, let's let's go on any other questions? I got, let's just answer one more, and then I'm probably gonna have...

56:56

A patient denies recent alcohol use. His blood alcohol concentration is negative, which of the following lab values is a relatively specific indicator of alcohol consumption, even after the blood alcohol level is negative. Is it enhanced serum sodium; GGT? I'll let you read them. So I don't have to say them. Elevated ASD and ethyl glucuronide?

57:20

D's and B's in the chat...

57:23

Yeah, the right answer is the ethyl glucoronide, ethyl sulfate's another one that we'll also look at. These are long lasting fatty acid, or glucuronidated form so there's also a fatty acid ethyl- ethanol link that you can look at. But these are these are produced quite rapidly in the body and lasts for days or many days after alcohol use. Whereas remember, alcohol we talked about is gone even in the heavier drinkers by you know, eight or 12 hours. These persist for days and are able to be measured. GGT is a marker for hepatic injury. So you're not going to go out and drink tonight and elevate your GGT. But if you drink for several days or longer, you might see a little bit of a blip in your GGT. So it is an okay answer that it will give you an indicator of alcohol consumption. It's pretty nonspecific. And you need a good history. Whereas the EtG is pretty specific. There's nothing else it's going to do.

58:29

But one concern you have with EtG is like your use of mouthwash, for example, that contains alcohol, that's how sensitive this test is. But of course, you will ask the patient these questions ahead of time, if you want to use it. AST is not as good as GGT as a marker for hepatic injury related to alcohol use. And of course, the elevated serum sodium is not particularly relevant. I mean, if you were, you know, dehydrated, or if you were using GHB that had a lot of sodium in it or something, it might be okay, but not in this model here. All right. Well, thank you. I'm gonna have to end Giulia, if that's okay, I hope. Are there any other questions?

59:11

Sorry- could not unmute myself, that is not a problem. We're right on time. So I appreciate you being here with us today, Dr. Nelson. And I appreciate everybody's attendance and participation. As a reminder, we're back next week, we're going to be talking about opioids and cannabis and all things pain related. So you know, if you have questions leading up to it, feel free to submit them. And we'll also be here for additional questions. Thank you all once again, and I'll see you all next week.

59:37

Thank you. Thanks, everybody.