Episode 85: Benzodiazepines and Alcohol: Does Cross-Tolerance Work Both Ways?

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Transcript

Welcome back to The Tox Lab. I'm Rebecca and I'm Rob. This week we're going to be asking a question. If I regularly drink a bottle of wine a night for 10 years and then I take diazepam, does the diazepam do anything?

It's a good question. Or if we reverse that, what if I take diazepam once a day for 10 years and then I drink a bottle of wine? Does the alcohol do anything? We're going to be unpacking this question this week, looking at this idea of alcohol and benzodiazepine cross tolerance and how exposure to one affects your reaction to the other.

Now we do have to give a shout out this week. This was a suggestion by Jennifer Harmon who wrote into us some time ago now asking us to cover this topic. So before we dive too hard into alcohol and benzos, I thought we could consider firstly what is tolerance in general and also explore this idea of cross tolerance in a little bit more general terms. So what is tolerance?

Tolerance is essentially the reduction in effect that you get when you're exposed to a drug over a period of time. And I don't know about you. I find, I suppose I have got a pharmacology background and I think about these things. To me, it feels quite innate, but I don't think it is necessarily something people actually think about.

Yeah. Because I had to explain this topic to a friend of mine recently. She's had ongoing issues with her knee. She was put on tramadol.

It helped for a while. After a while, the tramadol wasn't helping. So I said, what happened? And she said, well, I actually took myself off the tramadol.

And I said, well, it might work now. Yeah. You know, she's had weeks without the tramadol. She somehow came off them relatively easily, apparently.

But it's this effect that when you're exposed to a drug, the effect of that drug decreases. Now, cross tolerance is where you're not exposed to the drug that you're tolerant to, but you're exposed to something else. And it has a decreasing effect on other similar drugs. So I thought we could look at some cross tolerance topics and see whether just based on feeling, yeah, whether you think you're going to see cross tolerance or not.

Okay. So LSD and magic mushrooms. I think so. Yeah.

Yeah. So if you regularly take LSD, you then take magic mushrooms, you're probably going to get a blunted effect. And it's because the serotonin receptors in particular, the 5-HT2A receptor, you get down regulation and therefore less of an effect. Yeah.

Fine. How about alcohol and cannabis? Both cause sedating effects? Both lead to relaxation?

I think not. Correct. Yeah, correct. Although they have similar effects, they work through very different pathways and you're right, no cross tolerance.

What about nicotine and caffeine? Classic Italian breakfast? A double espresso and a cigarette? Cross tolerance there?

No. Well, interesting here because there is no receptor cross tolerance. Yeah. But smoking does increase your caffeine metabolism.

Okay. So if you are a smoker, you can tolerate more caffeine because you clear it faster. That's fair. Yeah.

So there's this interaction, but it's not classical receptor tolerance. And finally, the topic of today's episode, alcohol and benzodiazepines. Well, that's really what we're going to unpack this week. Before we dive into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab.

We also have a page on LinkedIn and we're fairly active over there. And for those of you who don't use social media, but still want to get in touch with episode suggestions or comments about episodes, you can check out our new website at thetoxlab.co.uk. So let's look at that first question. If somebody is a regular user of alcohol, where do benzodiazepines fit into this pathway?

So benzodiazepines are used to treat alcohol withdrawal. So according to the DSM five alcohol withdrawal syndrome is characterized by the reduction or cessation of prolonged heavy alcohol use, along with at least two of the following symptoms. And this includes autonomic hyperactivity, tremors, insomnia, nausea, hallucinations, psychomotor agitation, anxiety, seizures, or drinking to relieve these symptoms. And there are four distinct clinical alcohol withdrawal syndromes.

So you can get uncomplicated withdrawal, which manifests as tremors, nervousness, irritability. You can get withdrawal seizures, which typically occur within 12 hours after the last drink peaking around 12 to 24 hours later, and manifest as generalized motor seizures. You can get alcoholic hallucinosis, which can appear as early as eight hours after the last drink. And this manifests as visual misperceptions and tactile hallucinations.

And then the final one is delirium tremens, which we discussed a little while back in episode 69, if you want to go and hear more about that. Alcohol withdrawal can be as we've discussed before fatal. And so the use of benzos in this context really is lifesaving. So let's jump in into how alcohol and benzodiazepines kind of overlap and how benzos can be used to treat alcohol withdrawal.

So alcohol acts as a positive allosteric modulator of the GABA A receptors, which basically means that it binds to a different site on the receptor than GABA does and enhances the activity at the receptor. So when alcohol binds to its binding site on the GABA A receptor, it increases the duration and the frequency that the chloride channel in GABA is open for. And essentially, alcohol leads to an amplification of the effect of GABA, enhancing the sedative calming and anti-anxiety effects that you see. Let's unpack that slightly.

So the GABA-nergic neurons are what we call inhibitory neurons. So by stimulating or increasing the power of the GABA neurons, you're actually decreasing the overall activity within the brain. In the excitatory counterpart of GABA is glutamate, which acts on the NMDA receptors in the brain. And GABA and glutamate work together to kind of balance neurotransmission.

And when alcohol is used chronically, there is a downregulation in the GABA A receptors to counteract this increase in the activity. And there is an increase in glutamate levels and an upregulation of the NMDA receptors to help balance our alcohol's effects on the GABA A receptor. And this overall contributes to the development of alcohol tolerance. So when alcohol consumption is stopped abruptly, the enhanced inhibitory activity at the GABA A receptors is suddenly lost.

And at the same time, you get this increased excitatory activity of the glutamate at the NMDA receptors. And this becomes unopposed, leading to neuronal hyperexcitability. And this imbalance between reduced inhibition and increased excitation produces the signs and symptoms of alcohol withdrawal syndrome. So it isn't just the case of there's less GABA activity.

You've actually also, over a chronic period of time, developed this increase in the excitatory to balance out the fact that GABA was being revved up by the alcohol. Yes, it's like a balance that everything was working in harmony, essentially. And then you take one thing away and suddenly the scales are flipped. Treatment for alcohol withdrawal is focused on using other allosteric modulators of GABA A receptors.

And this includes benzodiazepines. And importantly, only 20% of cases need pharmacological intervention. And intervening unnecessarily can be harmful, leading to excistation, respiratory depression, risk of falls, disinhibition and delirium. So treatment is only recommended in complicated cases where seizures, hallucinations or delirium tremens are present.

Okay, so it is the most extreme cases of alcohol withdrawal. So why are benzos used? So benzos also act as an allosteric modulator of the GABA A receptor and are thought to restore the balance between the inhibitory and excitatory neurotransmitters by once again increasing the activity of the GABA A receptor and helping to control that excitation.

However, because chronic alcohol use leads to neuro adaptations that reduce GABA A receptor sensitivity and increase that excitatory glutamate signaling, benzos may be less effective at standard doses and higher doses are often required during alcohol withdrawal to control central nervous system hyper excitability. So this is the idea of cross tolerance that you've got alcohol affecting the GABA receptor and therefore you need a higher dose of benzodiazepines to have that same effect.

So someone who is regularly drinking, they've already down regulated the GABA A and therefore you bring benzos along, they will need more benzo to counteract the fact that they are already tolerant to the alcohol. Yeah, exactly. It is important to know that benzos do come with their own downsides, including respiratory depression, sedation, delirium, falls and paradoxical agitation. And it's important to choose the right benzodiazepine in these sorts of cases.

So long acting benzos such as diazepam and chlorodazepoxide are metabolized in the liver via side growing P450 enzymes and produce active metabolites. So in severe hepatic impairment, which you might get in someone who's chronically using alcohol, you get reduced oxidative metabolism which can lead to drug accumulation, prolong sedation and increase risk of toxicity. So often in these situations, the razepam is favored, it's primarily metabolized via phase two glucuronidation and does not produce active metabolites, making it often a safer option in patients with significant hepatic dysfunction. And that makes sense, doesn't it?

I mean, drugs like diazepam hang around for a very long time, got lots of active metabolites downstream, can produce an effect for quite a bit longer than the original diazepams detectable in the blood. Yeah. And you suddenly give that to somebody who's got pretty much no liver reserve. So it does appear that chronically using alcohol does give you a degree of tolerance to benzodiazepines, but do long-term benzodiazepines offer the same cross tolerance with alcohol?

And that was the question, wasn't it? We know that benzos are used to treat alcohol and we know that that can affect the dose, but does it work the other way? If somebody regularly takes benzos, what does a bottle of wine do, for example? So benzodiazepines bind to a different site to ethanol on the GABA A receptor, leading to an increase in the frequency of which the chloro channel is open for.

And with long-term benzodiazepine use, proposed mechanisms of tolerance include GABA A receptor uncoupling, which reduces the functional enhancement of GABA A signaling. And this can involve lots of different things, including receptor phosphorylation, altered trafficking at the receptor, changes in subunit composition, among many others. Additional adaptations include alterations in GABA A receptor subunit expression rather than simple receptor downregulation, as well as that compensatory increase that includes metergic signaling.

And because both benzodiazepines and alcohol enhance the inhibitory signaling at the GABA A receptor, benzodiazepine tolerance may confer partial cross tolerance to alcohol's sedative, anxiolytic, and some of the psychomotor effects in relation to its action at the GABA A receptor. The issue is alcohol acts on a number of different neurotransmitter systems beyond GABA A. This includes inhibition of the NMDA receptor function, modulation of glycine and serotonin receptors, effects on nicotinic astocranium receptors, and indirect effects on dopaminergic reward pathways.

Among many others, there's an absolutely massive list of the different ways that alcohol can affect those sorts of pathways. In other words, alcohol tolerance is not confined to just the GABA pathway. It actually hits a whole host of other receptors and does a whole host of other things. Whereas benzodiazepines are a lot more specific.

These additional actions contribute to NMDA-related cognitive impairment, increased dopaminergic signaling, underlying reward and euphoria, cerevular dysfunction leading to ataxia, and widespread cortical network suppression resulting in disinhibition, and these effects are obviously not prevented by benzodiazepine tolerance. And actually, there is a lot to be said for the complexities of benzo tolerance as well. Tolerance is not always complete tolerance to all the effects of a drug. Sometimes tolerance can be partial tolerance to some of the effects.

And you sometimes see that with benzodiazepines. People can become very, very tolerant to some of the sedative effects. People who regularly take benzodiazepines for, for example, anxiety. Initially, when they start taking the drug, they can find they're quite sedated.

They can be quite sleepy, quite impaired. Users can become quite tolerant to that effect fairly quickly. But studies have actually shown that they still have a degree of functional impairment that you don't develop tolerance to in quite the same way. It can affect things like memory in a different way to how it affects your sedation.

And so tolerance in that sense can be incomplete. It's not just a case of I take 20 mg of diazepam every day and therefore it doesn't affect me anymore. It can be I take 20 mg of diazepam every day and it no longer makes me sleepy, but it's still having some effects. So do we know why there's that difference in the tolerance as to how you can become tolerant to one part of the effect but not the other?

I think that effect mostly is through differences in GABA subunit expression. And so GABA receptors are not all one thing. You get different types of GABA receptor and they express different subunits and different parts of the brain express different subunits differently. And so you get an effect on some subunits more than others.

Okay, that makes sense. And so you do get this tolerance to some effects and less tolerance to others. It's not like, as opposed to the cross tolerance with alcohol, where a lot of the effects are not only because subunit expression is incomplete through benzos, but also alcohol is just doing so much other messy stuff on so many other receptors. So even though there does appear to be some cross tolerance between alcohol and benzos, when these are combined, there is a significant risk of respiratory depression.

And this is due to the synergistic central nervous system depression that you see with alcohol and benzodiazepine use involving that enhanced inhibitory GABAergic signaling and reduced excitatory drive within the brain stem respiratory centers. And this overall leads to a reduction in respiratory drive, impaired ventilatory response to carbon dioxide, progressive slowing of breathing, and this can be fatal. And this is probably the biggest problem we see in drug related harms related to alcohol and benzos. You can become tolerant to some of the sedatory effects.

Doesn't necessarily mean you're tolerant to the respiratory depression effects. And so it's interesting, isn't it? It seems to work more one way than the other. But that makes sense because alcohol is hitting all of these other receptors.

And one of those is the GABA receptor. Whereas you do it the other way, even though tolerance develops at the GABA receptor, alcohol is still doing all of its other messy stuff. So what is the future of alcohol? Is alcohol's place in society changing?

There's a general trend to people drinking less alcohol. Yeah, that's recognized. And that seems to be a thing, either people using other substances or people are just recognizing the harms of using alcohol and deciding that they don't want to drink. So a slightly off tangent thought I've just had, and you may not have any prep for this or have an answer.

So it might just be this becomes a future episode. You were talking about alcohol's role in NMDA receptor antagonism. What happens with alcohol and ketamine cross tolerance? I don't know.

It sounds like a good future episode. Absolutely. I think so. We might have to look into that.

Ketamine, famously, an NMDA antagonist. So here is a question then about tolerance. Is tolerance protective? I think it depends.

Explain. You can't just say it depends and leave it there. I say can. Well, as we've seen, it can protect against certain effects.

But as we know, interactions between different drugs is complex. So you're not always going to get complete and perfect cross tolerance and tolerance in general. It's interesting, isn't it? Tolerance is a physiological protective effect to exposure to something that upsets your brain chemistry balance.

And the brain tries to address that and effectively bring itself as close as it can to normal. The trouble is, is that tolerance often brings with it either reductions in medication effectiveness or dose escalation. And because of the fact that tolerance is often partial, and actually it can increase your risk of complications such as respiratory depression. We sort of see this with opioids.

As people's tolerance grows, yes, their respiratory depression ceiling grows with it, but it doesn't always grow at the same rate. And so that difference between an inverted commas recreational dose and a dose that would lead to significant respiratory depression actually narrows in people who are more tolerant. Another question I have for you, and maybe this is less of a thing now, actually. So I'm going to be saying this as an older person speaking to a younger person.

Yeah. Is having a high alcohol tolerance something to be proud of? Because I don't know, for me, culturally, when I was in my 20s, it was a bit of a brag. I think at least when I was at uni, it still was a brag.

If you could handle your drink in a significant amount of alcohol, you did kind of have bragging rights a little bit. When you say it out loud, it just makes no sense. I think it's just that uni college culture. Yeah, yeah, yeah, definitely.

This whole alcohol culture. And perhaps this is why the younger generation are now rejecting it. Okay, here's a controversial question. Do we over-medicalize anxiety, but under-medicalize alcohol?

By that I mean, if somebody has functional anxiety and needs diazepam to function, we think, hold on a minute, doctor, you shouldn't be handing out this much diazepam. On the other hand, if someone is functionally otherwise holding down a job and living a normal life, but drinks a bottle of wine at night, society just sort of treats that as normal, right? Yeah. And yet, well, probably objectively, the alcohol might even be doing more harm than the benzodiazepines.

I think that's fair. I think alcohol use is complicated. People, one, struggle to conceptualize how much they're actually drinking. And that's a big issue.

We know that when people go to their GP and they're asked how many units of alcohol do you drink a week, everyone under exit, because no one's got really any grounding to work out how much they're consuming. How many units are in a pint of beer? I should know this. I was going to say, you're a toxicologist.

If you don't know this, how does a random member of the public? One. At least two. See?

But it depends on, like, the strength of what you're drinking and things like that. It's not super easy for many people to work out on the spot when you're at your GP, but then if your healthcare professional doesn't know how much you're consuming, they're not necessarily going to signpost you to get help and seek treatment for that, if that's what you want to do. Whereas if you go to your GP, like, I'm feeling really anxious, I need medication, and that medication is helping, and then it doesn't and you use it up your day. So I feel like they have a duty to kind of help you with that.

So it gets messy. It is messy. Absolutely. And society's view of alcohol is, as you say, complicated for sure.

How much is too much? There is no clear answer to that. I think it's interesting why society views these things differently. I feel like we've rabbit holed a bit off of the pharmacology into discussing the general differences society perceives of alcohol versus benzos.

But it is interesting. It's often said that if alcohol were discovered today, it would be banned. Yeah. And I don't know how true that is, but it is fair to say it is one of the leading causes of health-related harms, related to drugs in particular.

You know, it's just so available. And even in people who perhaps don't consider themselves to have alcohol use disorder or tick any of those criteria, it's still a leading cause of fatty liver and other metabolic complications, even if you just factor in the fact that three or four points could be quite a significant calorie load, if nothing else. So it is a real societal problem, and yet it is considered to be just part of life. So converse point then, have we become too afraid of benzodiazepines?

I think it depends who you ask. I mean, that's probably fair. I think it is reasonable to say that they're probably not an ideal solution to long-term anxiety. And I think as we learn more about the harms of certain medications and being on certain medications for a long time, and interactions and all these different things, you do kind of see the downsides more than the benefits.

And then I think there is a drive to find things that provide that benefit with less downsides. I think that's completely fair. So I mean, benzos broadly replace the barbiturates, and it's completely fair to say that benzodiazepines have a lot less acute toxicity than barbiturates. Do they still have similar long-term complications?

Yeah, they do. I guess the dream would be a drug which reduces anxiety without leading to tolerance, leading to dose escalation. Maybe in the complexities that is GABA subtypes, maybe there is something out there. Maybe there is something that could affect a particular GABA subtype in a way that benzos don't currently.

I don't know. Maybe there is something that's yet to be discovered. So going back to our original questions then, if I regularly drink a bottle of wine at night and I take some benzos, will the benzos have an effect? They'll have less of an effect.

Yeah, fair. And the other way, if I regularly take benzos and have a bottle of wine. I think you'll still feel it. I think you're probably right.

I think you're probably right. Well, I hope you've enjoyed listening to us this week because we've rabbit holed a little bit on alcohol and benzos. I've certainly had a good chat. It's been good.

Thank you again, Jennifer, for suggesting this episode this week. We've really enjoyed having a look at this topic. And if anybody's listening who has got some episode suggestions and want to reach out to us, please do get in touch. Hope you'll have an amazing week and we'll see you next time.

Bye.