Episode 80: Novel Benzodiazepines - Emerging Trends and Analytical Challenges

Transcript

Hi everyone, welcome back to the Tox Lab.

I'm Rebecca.

I'm Rob.

This week, we're going to be taking a look at the subject of novel benzos. We've talked about novel benzos two or three times on this podcast, haven't we?

Yeah. And they're a subject that I've had an interest in for quite some time. And very recently, a very large paper looking at the phenomenon across toxicology has been published. And this was published by the SOFT NPS committee, I believe, so the Society of Forensic Toxicologists. And this week, we're going to take a dive into that paper and have a look at the strange world of novel benzos. Before we dive into the science this week, I thought we'd have a look at what novel really means. So Rebecca, I'm going to ask you a few things.

You tell me if they're novel or not.

Okay.

Air fryers?

Less novel.

Less novel?

Yeah.

Oat milk? I don't think that's novel anymore, no.

No, so oat milk's been around for a while. I feel like oat milk's more mainstream than it used to be.

But it used to be novel. Because spoiler alert, I used to work as a barista. And when I used to work as a barista, oat milk was not an option.

No.

DVDs?

Clearly not novel.

Definitely not novel.

Definitely not novel. And so this idea of what is novel really does change over time. And going back then to the subject of novel benzodiazepines, what even makes a benzodiazepine novel anymore?

That is a good question. You've not been in toxicology as long as I have.

No. Do you remember a time pre-novel benzodiazepine?

I don't think so. Because when I started, like we had bromazolam as being a very prominent novel benzo, and I don't remember a world before that was a thing. So I'm going to put to you that some of these novel benzos, perhaps a bit less novel.

Yeah. But nonetheless, we are going to look at the paper looking at this phenomenon of novel benzos and unpack whether we think they're novel or not and where we think things are going. Before we jump 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 for episodes, you can head over to our new website, thetoxlab.co.uk. And one more plug, we're not going to be releasing an episode next Monday, but we are hoping to do a live stream, our very first Tox Lab livestream on the Tuesday to correspond with the European Drug Agency's annual drug report. If you're around that evening, do come and join us as we unpack that report together.

Assuming the tech works.

Fingers crossed. It may all go horribly wrong, but we're going to give it a go. So before we dive into novel benzos, very, very brief primer on benzos in general. So benzodiazepines were essentially invented by accident in the 1950s, a person called Leo Sternbach at Hoffman LaRoche was working on new tranquilizers and they stumbled across chlordiazepoxide, marketed as Librium. Chlordiazepoxide is still used today occasionally, not as often as it was, but this really brought in this era of benzodiazepines and they are sedative drugs.

They are used to treat anxiety.

They're used to treat seizures. They've got quite wide medical use as sedatives. And the context at the time was that at the time, the best available sedatives were barbiturate drugs and benzodiazepines were considered to be a safer alternative. So they then saw this rise in popularity. Following on from chlordiazepoxide in the 60s, they discovered diazepam marketed under the brand name Valium and that's probably the benzo that most people have heard of. And then throughout the next 10, 20 years, huge expansion of benzodiazepines. So things like nitrazepam, lorazepam, temazepam, clonazepam, all of these medicinal benzos saw therapeutic use in different forms.

Some of them were longer-acting.

Some of them were shorter-acting benzodiazepines. And they all saw different medicinal uses in different situations. And as we've heard, this story's repeated quite often. These drugs for a while were great. And then people started to see dependence and withdrawal. And suddenly they realized that there may be a bit of a downside to their use. And so the use kind of did get tailed off a bit, but they still did see quite significant medicinal use as they do today. But in the 2000s and really early 2010s, we started to see the rise of, in particular, internet drug markets. And this is where non-pharmaceutical benzodiazepines started to emerge on the scene. And that's where this week's paper starts to take off. There are lots of different origins of novel benzodiazepines. So some are benzodiazepines that are legitimately prescribed in other countries but are taken illicitly in others. Some are chemically modified from existing drugs. For example, bromazolam and flualprazolam are halogenated alprazolam derivatives. And some of them are targeted active metabolites of prescribed prodrugs, such as desalkylgidazepam. And actually, we should have given this health warning earlier on. We are gonna be saying a lot of complicated chemical names and they all do sound very similar, for which I apologize, but there's no other way, really, of describing these things. So as Rebecca said, bromazolam is a version of alprazolam.

Alprazolam is a legitimate pharmaceutical. Under the brand name Xanax, a lot of people will have heard of it. Bromazolam is essentially an alprazolam molecule where the chlorine has been replaced by a bromine. So chemically it's very similar, but it's also different. And the pharmacological effects of these novel benzos are related to its structure, as this will alter how it binds to the receptor, which then impacts potency and its overall biological activity. And many of these novel benzos are more potent than traditional benzos, for example, etizolam. It's thought to be approximately 10 times more potent than diazepam. And let's unpack etizolam a little bit, because as you hinted at, etizolam is actually a legitimate medication in a number of countries. But it did also see its place in these novel internet drug markets, which was being synthesized not as a pharmaceutical, but as a chemical, and ending up in pellet form, as well as probably existing as diverted medications at the same time. And novel benzodiazepines are a bit of an unusual subclass of novel psychiatric substances. So traditionally we see novel psychiatric substances coming in waves, whereas a lot of the novel benzos kind of hang around and stay around for quite a while.

I think that that's true. I mean, up to that point, prior to the novel benzo market, we had the novel stimulant market, the cathinone market. And that really was punctuated by the emergence of a compound, often the control of that compound, followed by the emergence of a slightly different compound. And you're right, novel benzos don't really seem to have done that. There has been a bit of a pattern. There certainly are novel benzos that I now don't see.

Some have clearly come and gone.

Yeah. But what is interesting is some have also stuck around. And every so often you're surprised by an old one. And I think some have stuck around despite international controls being put in place, which for, I don't know whether it's fair to say, for other classes of drugs, there tends to be a control and then something else takes its place.

Possibly teasing a future episode there. But yeah, that is generally the trend that has been seen, although I think it probably does vary depending on the class of drugs. So surveilling the use of novel benzos can be a really big challenge due to differences in naming conventions of the benzodiazepines and laboratories not including novel benzos in their testing repertoire. And those that do don't necessarily publish their findings leading to under-reporting of their prevalence. So the Society of Forensic Toxicologists, NPS Committee aim to review published effects, observations and toxicological data in both forensic and clinical settings for novel benzos between 2021 and 2025. So for this narrative review, they conducted a systematic review of the literature and included 223 articles and 36 abstracts related to NPS benzodiazepines. And they break down their data into post-mortem work, clinical cases, driving under the influence of drugs and drug-facilitated crime. And I really highly recommend this paper. It's a really great resource for all the different studies and publications around this topic. So if you do have an interest in novel benzos or have a case that you wanna put into context, I would recommend checking this out. So first, taking a look at novel benzos in post-mortem cases.

Novel benzos are often found in combination with other drugs, most commonly opioids, including fentanyl, carfentanil, and nitazenes. So this combination of typically fentanyl and benzos is known as benzodope and is quite a phenomenon in the US. So just to put that into a little bit of context, this is true of pharmaceutical benzos too.

Yes. In general, benzodiazepines, although they may contribute to respiratory depression in opioid overdoses, in general, most of the time, they rarely lead to fatal overdose in and of themselves. And novel benzos are also seen with stimulants such as cocaine and methamphetamine. And when novel benzos are taken at higher doses, they can be used to lengthen and possibly intensify the euphoric effect of opioids. And individuals may also use these to self-medicate to reduce withdrawal effects

from opioid stimulants or hallucinogens. So taking a look at bromazolam first, this first emerged in Europe in around 2016 and was identified in the US in May, 2020. By the end of 2022, it replaced etizolam as the predominant designer benzo in the US. I remember my first case of bromazolam because we were still using benzodiazepine immunoassays. And I knew I had a benzo in my sample. My benzo screen on the mass spec was negative. I ended up doing untargeted screening using a triple quad. Don't let anyone tell you, you can't do untargeted work with a triple quad because you can, but you probably shouldn't. It was a lot of work, but we got there, we solved it. Case reports from British Columbia, the UK and across the US had been reported. Nearly every case contained at least one other additional drug. In British Columbia and the US, fentanyl was the main co-detected substance and methamphetamine was also frequently co-detected. In a UK data set of 96 cases, all but one contained another drug and gabapentinoids, cocaine and diazepam were the most common and no fentanyl was reported, which kind of lines up with what we see in the UK. Generally, we don't see fentanyl in the recreational drug supply. It's not never, but it's not as prominent as it is in the US. We certainly haven't seen the fentanyl wave that the US saw. While the US was seeing a lot of fentanyl, we were still seeing heroin. And 46% of these cases contained another NPS benzo and etizolam and flubromazolam were the most common. So moving on to clonazolam, this wasn't widely reported over the five years and clonazolam is highly unstable and often its metabolite eight amino clonazolam is reported qualitatively in case work. There was a case report from Germany of a 21 year old where the death was attributed to polydrug toxicity. And in this case, there was evidence of heroin use, flualprazolam and a synthetic cannabinoid alongside clonazolam. Clonazolam was also reported in a case of a 14 year old who had reportedly ingested 12 Xanax tablets and no alprazolam was detected in this case. And that actually takes us on to a fairly substantial point, doesn't it? That these drugs come in lots of forms. You've talked about benzo dope and how in the US it was sometimes mixed in with opioids. But it also took the form of counterfeit pharmaceuticals. And I think this tended to be a later phenomenon in the novel benzo era. Initially, the internet drug markets were selling powders and pellets. And these, as far as I understand, were broadly what they were sold as. If it said you were buying etizolam, you were probably buying etizolam. But later in the phenomenon, probably 2016 onwards, we also started to see counterfeit benzodiazepines. They look like Xanax bars or even they look like foiled blister packed diazepam. And they can be really, really convincing counterfeits. Like you look at pictures of counterfeit benzo seizures and they're foiled perfectly.

They've got all the text. You've got the inserts from the packaging in there and everything. You have to know what you're looking at and probably do lot number comparisons and so on to actually be able to spot these as fakes.

They're really good fakes. Qualitative reports of clonazolam were often alongside nitazenes, such as metonitazene and fluonitazene. Other NPS benzodiazepines, such as flualprazolam and pyrazolam, and alongside some synthetic cathinones.

Moving on to desalkylgidazepam. This was first detected in British Columbia in April, 2022. And there were 74 post-mortem cases that were identified where all but one were found to involve other drugs. And fentanyl or norfentanyl were confirmed in 96.8% of cases. And I believe we covered this paper in one of our very first episodes. I do remember it was, gosh, fairly early, wasn't it?

Episode 12 or something like that.

In episode four.

So very, very early on.

46% of these cases involved desalkylgidazepam.

It's the only benzodiazepine detected. But bromazolam and etizolam were the most common benzodiazepines present when there was a co-detection of benzodiazepines. We've also detected desalkylgidazepam in one case alongside N-pyrrolidino isotonitazene, bromazolam, pregabalin, and tramadol. And we've recently published this as part of our N-pyrrolidino isotonitazene case series, which I will also link in the description below. Moving on to etizolam, which was one of the more popular NPS benzos in post-mortem case work and has been reported quite widely over the last five years. It was most commonly found alongside fentanyl, other benzodiazepines, both illicit and licit, ethanol, over-the-counter meds, stimulants, cannabinoids, opioids, opiates, and nitazenes. And there have also been no etizolam-only reported fatal cases in the literature between 2021 and 2025. And as I said earlier, etizolam is actually approved as a medicine in some countries. So even though in some countries it's emerging as a novel benzo, it is approved for pharmaceutical use in some parts of the world. Etizolam is an interesting phenomenon in the UK because it shows the regional variability you see with some of these drugs because etizolam was particularly prominent in Scotland.

Okay. And yet in the Southeast, we were barely seeing it. We had a handful of cases, but apparently it was really common in Scotland. So looking next at flualprazolam, this is the 2-fluoro derivative of alprazolam and was first reported in the literature in 2019. This is an alprazolam molecule with a fluorine attached. And in a case series of 1,250 benzo dope cases in Alberta, Canada, 375 contained flualprazolam in combination with fentanyl. And again, flualprazolam was not detected on its own and was frequently detected alongside fentanyl or other opioids. When looking at flubromazolam, there was only one case reported between 2021 and 2025. And this case involved a 30-year-old male with mental health issues and a history of suicide attempts. So he was also receiving methadone treatment. Peripheral blood was analysed and flubromazolam was found at a concentration of 418 nanograms per millilitre alongside the opioid U47700, also known as pinky or pink heroin, and was also detected alongside methadone and diazepam. And we have got to do an episode on U-series opioids.

Yeah. It's no longer something that we tend to see, but they had some rather unusual side effects described in the grey literature. So looking at flubromazolam, this wasn't widely reported. And there was one case series where flubromazolam was detected in 137 death investigation cases between the 1st of July and the 31st of July 2021 in Ontario, Canada. And 17% of these cases reported both the presence of flualprazolam and flubromazolam. And all cases also had at least one other substance detected. Again, most commonly opioids such as fentanyl and methadone. Moving on to some less commonly detected ones, pyrazolam was the first NPS benzo reported back in 2012 and is occasionally detected in post-mortem casework alongside opioids. So very similar to the other novel benzos that we've seen. And rilmazepam is the prodrug for active metabolites, rilmazepam, didesmethal, rilmazepam, and carboxy rilmazepam. And two cases have been reported in Sweden despite rilmazepam not being an approved medication in this country. And this shows another one of the chemical tricks instead of creating new versions of active drugs, creating compounds that are metabolized to active drugs. So when looking at the clinical studies, there were 10 observational studies and 17 clinical case reports that were included. Patients within the case reports had a median age of 31 years and the individuals were predominantly male. And the substances that were claimed to have been ingested were often counterfeit medications such as counterfeit Xanax. When looking at the observational studies, there were clear geographical differences in the benzos that were seen. So meclonazepam and 4-chloro-deschloroalprazolam were only reported in the US, whereas desarcargodazepam and nitrazolam were only reported in Australia, while bromazolam, clonazolam, phenazepam, and etizolam were reported across multiple countries. And in terms of the polysubstance use that comes along with novel benzos, there were also geographical differences, with stimulants being frequently co-detected in Australia and the UK, while in the US opioids such as fentanyl were the most commonly co-detected drug. And this is a similar pattern to what we've just

discussed in the post-mortem work. When looking at the clinical case studies, case studies for bromazolam, clonazolam, etizolam, flualprazolam, flubromazolam, and pyrazolam were included. And individuals were most commonly presenting to hospital with CNS-depressant symptoms, which fits with what we know about benzodiazepines. And unlike in the post-mortem case work, there were several cases where the NPS benzo was the only detectable substance, which was extremely rare in the post-mortem work. And I think this takes us back to people not publishing their data, because I've definitely had some clinical cases involving novel benzos. And you're right, unlike in the fatal cases, these were single-drug administrations, and these people were admitted to hospital. They were often in a confused state or a sedated state, often in hospital, sometimes for two or three days. I remember at least one patient who had a very prolonged presentation. He thought he had taken significant overdose of diazepam.

No diazepam detected.

We detected flubromazolam. And he was definitely in hospital for a few days before being released. But as you say, unlike the fatal cases, it was just that one drug. I think this particular case sticks with me because at the time there was very little known about flubromazolam, but there was a reasonable amount reported in the gray literature. So things like Reddit users saying flubromazolam's got a very long half-life. And so we took that to mean actually the fact that it was still sedated three days later is perhaps consistent with what other people are describing.

That is interesting. I think it highlights the importance of when you've got cases like this of trying to get them published just so that when other labs are seeing a very similar thing, they can kind of put their findings into context. And I think this paper really highlights that there is a gap in what is out there. Give me an extra day a week to write up everything interesting.

That's a fair point too. So moving on to driving under the influence of drugs, NPS benzos can lead to impaired mental function, prolonged reaction time, slurred speech and loss of motor control, which all impact on one's ability to operate a motor vehicle safely. Their presence in driving under the influence of drug cases often involve erratic driving, collisions and observed impairment, including horizontal gaze nystagmus, which is the involuntary side-to-side jerking of the eyes when tracking a moving object and poor coordination. And novel benzos are often co-detected alongside other substances, which is a recurring theme, which then complicates interpretation of blood concentrations in these cases. Interpretation of blood concentrations in these cases becomes an absolute minefield, doesn't it? We know that benzodiazepines, pharmaceutical benzodiazepines can impair one's ability to drive. To what degree and to what degree a blood concentration indicates impairment really depends very much on somebody's tolerance.

Yeah, that is a really good point. That applies to drugs like diazepam that we have studied for many, many years and have written countless papers over. When it comes to these new benzos, we have literally got no idea how a blood concentration translates to impairment. And it really shows the importance in these cases of actually law enforcement officers collecting evidence of impairment beyond relying on the blood result. Because actually that blood result may not be able to tell us all that much beyond the presence of the compound. So moving on to drug-facilitated crime cases, novel benzos are thought to be fairly desirable drugs in the world of drug-facilitated crime because they're active at low doses, they're fast acting, they're easily orally administered and may have short half-lives leading to rapid metabolism and excretion. And there aren't that many published studies available looking at drug-facilitated crime and novel benzos. One study looked at 10,000 cases submitted for toxicology testing in Ontario, Canada between November 2019 and December 2020. Etizolam was quantified in 191 cases but only four of these were described as drug-facilitated crime. And it's thought that novel benzos in drug-facilitated crime is a much larger problem than is represented by

what's out there at the moment. And it's kind of compounded by a couple of different issues. There are often delays in reporting in drug-facilitated crime cases. So many novel benzos can become undetectable by the time a sample is taken.

Novel benzos are also not always included in scopes of lab testing at hospitals where people might be presenting. And the higher potency and shorter half-lives of novel benzos compared to traditional benzos means that there's a need for highly sensitive analytical methods which not every lab that's in a hospital will have access to. Actually going back to the metabolism issue, it possibly gets a bit more complicated than that because my understanding is that flubromazolam actually has active metabolites.

Okay. And that's probably true of a few others as well. So even though the parent drug might be undetectable, that doesn't mean the drug isn't still having an effect via downstream metabolism. If you look at a drug like diazepam, it's got fairly large number of active metabolites. And some of these novel benzos may well be doing similar things in terms of their metabolism. So this paper concludes quite nicely with the analytical challenges of looking for novel benzos. So one of the points that's brought up is that immunoassay screening methods vary in their cross-reactivity for the novel benzos. So some typically have higher cross-reactivities and some really poorly cross-react. So therefore, for a lot of the novel compounds, they might not be reliably detected. And immunoassays are quite a common screening method for hospitals when people are presenting to A&E, for example. This takes us on to a slightly different point actually going to the clinical picture. I had a conversation with an addiction psychiatrist colleague many years ago, and I was trying to sell our novel benzo service to him. And I said, look, we can tell all these different benzos apart. And he said, in his practice, and we are going back a few years, practice may have changed. If an individual comes in and they say they're dependent on benzos, they get them to pee in a cup and they dipstick it. If the dipsticks positive for benzos, they give them benzos. If you're addicted to a benzo that doesn't cross-react with your dipstick, you are in a pickle.

Yeah, for sure. And it's possible practice has changed a bit. And clearly, instrumentation and ability to deliver some of these more advanced screening tests has probably grown. But it does leave a potential clinical gap. And even when using like better techniques like mass spec, unpicking structural isomers can be a real challenge. So for example, we're looking at Alprazolam and 4-chloro-des-chloro-Alprazolam. This is a really big challenge and requires either high resolution mass spec, where you can look at the fragments. So the 165 fragment is more abundant for Alprazolam compared to the 131 fragment, which is more abundant for 4-chloro-des-chloro-Alprazolam. Or you do need optimized chromatography, which is also a challenge when you don't really know what you're looking for. And if you don't know that there is a structural isomer out there, you're not necessarily gonna have been able to optimize your chromatography to distinguish between the two. The stability of novel benzos is also an issue. So for example, clonazolam is highly unstable and is rapidly converted to its metabolite 8-amino-clonazolam. And this also goes for other benzos like clonazepam, which is rapidly metabolized to 7-amino-clonazepam. So it's important to include these metabolites in screening methods to help increase detection windows. But as we've talked about before, some of the metabolites are being sold as novel benzos in and of themselves. So it doesn't necessarily point you to the parent drug as being the drug that was used. So interpretation can get a bit tricky. Going back to the nitro benzos, there's another good point actually, and that's to do with post-mortem microbiome transformation. So in a post-mortem sample, you might not see any parent compound at all because in post-mortem blood, nitro benzos are often converted to their amino versions. And a lot of the novel benzos undergo glucuronidation. So flubromazolam, clonazolam, etizolam, and deschloro-etizolam are glucuronidated, and this is catalyzed by the enzyme UGT1A4.

And this enzyme is highly polymorphic. And so because of this, you can see differences in what is included in the urine because people will glucuronidate different amounts of that benzo. So when looking at interpretation of a measured concentration of these novel benzos, there are many challenges. One being that these are often used alongside other drugs. So what that level actually means in terms of the effects that are being seen is quite hard to unpick. And in the post-mortem world, post-mortem redistribution for a lot of these drugs isn't known. So the number that you get once you've quantitated that benzo is possibly a little bit meaningless. There's very little to interpret these numbers against.

Now all in all, I think this paper did a really good job of looking at the published literature on novel benzos. But I actually want to talk a little bit about an area that I find fascinating. And that is the unpublished literature because novel benzos in particular seem to take up quite a lot of space on internet drug forums like Reddit. And actually before we had a lot of these publications, that really was the only source of pharmacological knowledge we had.

People hadn't done receptor studies.

People hadn't done any real analysis. But what they had done is people on the internet had taken these compounds and reported their experiences online. And I think you see or saw at least quite a few themes emerge. Firstly, a lot of people were reporting taking these compounds not so much recreationally, but almost therapeutically to deal with underlying anxiety that perhaps their GP wasn't taking seriously and people generally trying to escape from mental health issues. But you also got a real sense of some of the issues that come with some of these compounds. I mean, you've talked about how some of these drugs were more potent than the pharmaceutical versions. Drugs like clonazolam would report huge amounts of amnesia. Users would describe taking a single dose and then losing 36 hours of their life.

Oh, wow.

Just because their memories didn't form. And some of these stories that you would see on Reddit actually were quite revealing. Obviously, we've no idea if any of this is true. This is all published anonymously on Reddit. But it did provide a real potential unverified source of insight. And what I also found interesting was there was quite a supportive community. A lot of people talking about tapering doses and how they could withdraw from these compounds safely because benzodiazepine withdrawal, as we've talked about before, can be fatal if not done safely. So I have always found the online communities discussing novel benzos to be particularly insightful. So going back to the original topic then, Rebecca, are novel benzos air fryers or DVDs?

That's a good question. I feel like a lot of the novel benzos are now less novel and they've been around for quite a number of years.

Yeah, generally less novel. We are still seeing the emergence of novel benzos, like ethyl bromazolam, that is starting to appear on the recreational drug markets. So novel benzos are still a thing. But I think a lot of the ones we talked about in this paper are a little bit more old school. I think we should change the phrasing actually. I think we should be talking about non-pharmaceutical benzodiazepines.

Yeah, that's probably a better way of phrasing it. Because you're right, they haven't gone away.

They haven't disappeared.

They are part of the landscape. Sometimes people are taking diazepam, sometimes people are taking bromazolam. They're no longer new compounds or even the concept of non-pharmaceutical benzos is not a new concept. But you're right, new ones do keep emerging. Ethyl bromazolam, relatively recent,

potentially new ones just around the corner as new. In fact, I think I saw ethyl flualprazolam has been detected somewhere recently. I can't remember where I saw that. So clearly new ones are still emerging. But this idea of non-pharmaceutical benzos appearing as a new drug market has now just become really part of the landscape. So if someone says to you they took a Xanax, what does that mean in 2026? I mean, I'd almost be surprised if there was any alprazolam there.

That's true in the UK, because of course alprazolam is not prescribed in the UK.

In the US it is. But still, I think it always warrants a deeper dive into what's lurking underneath. And I think more and more we are seeing really, really good counterfeits with more potent benzos, or indeed other drugs we've talked many times about the presence of novel opioids in counterfeit benzos, which is the thing that always really terrifies me. So it's definitely one to think about just because it looks real and it's printed as a Xanax bar and the packaging is perfect doesn't necessarily mean that's what is present. I think that's a really good point. I think that pharmaceutical branding and pharmaceutical lookalikes, I don't know, do you think they carry more risk?

I think so, because if you're buying something online and you think you're buying say alprazolam or diazepam and you think it's a legitimate pharmaceutical because the packaging is perfect, you're going to be more trusting that that is what you're going to be taking. And you don't necessarily think about the risks. Whereas if you're buying a couple of random pills in a little bag, I don't know, from my perspective I'm going to be like, well, I could be getting anything. I think that's fair, you know, go on the BNF and I'll say, oh, I can take 2 mg of diazepam because the BNF says I can.

Yeah. Except it's not 2 mg of diazepam, it's 2 mg of bromazolam or whatever.

Yeah, I think that's a really fair point. This idea of pharmaceutical branding can falsely reassure people that what they're taking is a legitimate pharmaceutical. I want to look a little bit at bromazolam because bromazolam has become, I think, probably the loudest of the benzos. It's certainly had, in my experience, the longest life.

Why?

Why is that?

Why bromazolam?

I don't know. I'm assuming that users enjoy the way bromazolam feels compared to other novel benzos. I know some just never took off because of user experience and I think bromazolam just fits what people are after when they're looking for a novel benzo. It's probably, pharmaceutically, quite similar to alprazolam.

Yeah. As opposed to other compounds, although we don't really know that, I don't think. So where is this not novel benzo market gonna go next?

What's your prediction? Ooh, that is a good question because if you asked me a couple of years ago, I would have said that bromazolam was gonna disappear after it came under international control, but we know that's not the case because we're still seeing it. I have a feeling bromazolam's gonna stick around and still be a really prominent novel benzo.

What about you?

What do you think?

I think it's really hard to predict, actually. I would never have predicted, like you, the long tail that bromazolam has had. Similarly, some compounds like flualprazolam, there was a run-on and suddenly

you don't see it again. I think it's possible we will see newer compounds emerge. How long they will stay for, whether we will see a new bromazolam contender or whether we will just see continual churn in the background of existing ones. I think what always surprises me is where a really old blast from the past appears. And you see something you really weren't expecting and haven't seen in five, six years. So if, like you say, novel benzos are now part of life, what's our responsibility as toxicologists? I think we have a responsibility to make sure our libraries are as complete as they can be for detecting novel benzos. I think when we do see clusters, if possible, it'd be great if we can get better as a community at trying to get the word out that these are being seen either through formal peer review publications or just by sharing things. There's a lot of toxicology forums and email chains going around, but I think that information is really important to make sure that people are aware of what's out there and what's one state over, for example, in the US or what's being seen up north in the UK. I think we are getting better at that. And I think we're possibly the best at it we've ever been.

Yeah, for sure. So I think there has been quite a lot of improvements in that regard, but I think you're right. On the other hand, it is hard, isn't it?

It's hard enough staying up to date with everything else that's going on. Keeping your libraries up to date can be challenging.

It's always changing. You just feel like you're always five, six steps behind. So that takes us on to my next question. How can we be more proactive rather than reactive?

Or can we?

Maybe we can't.

I don't know.

It's really challenging. And I think for some drug classes it's a little bit easier than others. For benzos, as you've got that halogenation, you can almost predict that there's gonna be the swapping out of the halogen until you get a non-halogenated version. And then everything goes out the window. I'm not sure there's an easy answer to that.

There isn't.

There really isn't.

Beyond what you've suggested.

So, no, don't feel bad. Well, thank you again to the Soft MPS Committee for putting this publication together. It's been a really enjoyable read for me and it's definitely given me a few things to think about. As always, it will be linked in the episode description below. And I hope you've enjoyed tuning in this week. Do give us a like, give us a follow. If you're hoping to join the live stream next week, do go and follow our YouTube channel in advance so you can get notified when we go live. We will put some timings out a bit closer to the time once we know what we're doing. Hope you will have an amazing week and we'll see you next time.

Bye.