THE TOX LAB

Podcast Transcript

Episode 4: Bromazolam and Desalkylgidazepam

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TRANSCRIPT

Hi everyone, welcome back to The Tox Lab. I'm Rebecca.

I'm Rob. Today we're going to be looking at a couple of papers on designer benzodiazepines, specifically bromazolam and desalkylgidazepam.

But before we jump in, I wanted to have a very quick chat about what benzodiazepines are in general.

Benzodiazepines are commonly prescribed pharmaceutical drugs, usually used for anxiety, insomnia, seizures, and muscle relaxation. They became widely used from the 1960s onwards and were initially seen as a relatively safe alternative to some of the older sedatives.

Over time, though, it became clear that they also have abuse potential and can cause dependence, tolerance, and withdrawal.

What we're looking at today are designer benzodiazepines. These are compounds designed to act like benzodiazepines but which were not necessarily approved for medical use. In some cases they were synthesised years ago and never marketed; in others they were made more recently as grey-market or illicit drugs.

We have seen a rise in these compounds over recent years. They are sold as counterfeit medications, sold online as research chemicals, and sometimes show up mixed into opioid supplies, especially in North America.

In the US, mixtures of opioids and benzodiazepines are sometimes referred to as "benzo-dope."

So Rebecca, why don't you take us through the first paper on bromazolam?

The first paper is titled The rise of bromazolam in post-mortem cases from Travis County, Texas, and surrounding areas, 2021 to 2023.

A little bit of background first. Bromazolam really started to emerge in the illicit market around 2020, especially after regulation tightened around other novel benzodiazepines such as etizolam and flualprazolam.

It was originally synthesised decades ago, but it was never approved for clinical use. Pharmacologically, it behaves broadly like other benzodiazepines, causing sedation, loss of coordination, slurred speech, dizziness, muscle relaxation, and potentially respiratory depression, especially when mixed with other depressants.

By October 2023, bromazolam had been placed under surveillance by the World Health Organization and was being considered for international control.

This particular paper looked retrospectively at bromazolam-positive post-mortem cases from Travis County and 46 surrounding counties in Texas, covering the period from 1 January 2021 to 31 December 2023.

During that period they had 7,129 post-mortem cases with toxicology, and 112 of them were positive for bromazolam, which works out at about 1.6 percent.

So it had become fairly prevalent in that post-mortem dataset.

Yes, and importantly it was increasing over time. The authors identified a statistically significant increase in bromazolam detections over the study period, and they also reported around a 7.5-fold increase in bromazolam-related deaths.

So not only was it being detected more often, it was also increasingly being considered contributory.

Exactly.

What did the demographics look like?

About 71 percent of the bromazolam-positive cases were men, with a median age of 31. The ethnic breakdown was broadly representative of the underlying regional population, so there was no obvious disproportion by ethnicity in this particular dataset.

Most of the deaths were classified as accidental. A smaller number were suicides, homicides, or natural deaths.

The homicide category is interesting, but I do not think it means people were being murdered with bromazolam. It probably just means bromazolam happened to be present in some homicide cases because the drug had become reasonably prevalent in the local drug supply.

That is how I would read it as well.

What about concentrations? Did the paper give much interpretation?

Not really enough to draw strong conclusions. There was a broad range of concentrations reported, but, as with most post-mortem benzodiazepine papers, there was a lot of overlap between cases where bromazolam was considered contributory and cases where it was simply present.

There was one case in which bromazolam was considered the main cause of death, but that case still sat within a concentration range that overlaps heavily with the other cases.

So we are not dealing with a neat "above this number it is fatal, below this number it is not" kind of situation.

No, and with benzodiazepines in general that is rarely how it works, especially post-mortem.

Looking at the cases overall, around 81 percent were considered to have bromazolam as a contributory factor. But 99 percent of bromazolam-positive cases had other drugs present as well.

That is the key point for me. Benzodiazepines, including prescribed ones, rarely cause fatal intoxication on their own. The real issue is what happens when you combine them with opioids, alcohol, or other sedatives.

And in this dataset, fentanyl was detected in 69 percent of the bromazolam-positive cases. Amphetamine was present in about 40 percent, and around 35 percent had other benzodiazepines present as well.

So bromazolam is appearing in a heavily polydrug context, especially with fentanyl.

Yes, and that fits with what has been seen more broadly in the US, where bromazolam has emerged not just in counterfeit tablets but also mixed into opioid supplies.

The paper also noted that the pattern of co-detection changed over time. Fentanyl co-detection increased during the study period, peaking around late 2022 before easing somewhat in 2023.

That could reflect changes in supply, enforcement, or local market preferences.

They also noted a fairly steady level of stimulant co-detection, things like cocaine and amphetamine, which is interesting because it suggests bromazolam is not only being encountered in "downer" contexts.

Yes, and that brings up another risk. If people are using stimulants and benzodiazepines together, they may end up using more of one because the subjective effects of the other are partially masking them. That can increase the risk of overdose, agitation, cardiovascular stress, and all sorts of complications.

So how does this compare with the UK picture?

There are UK post-mortem data showing bromazolam too, and although the exact co-detection profile differs, the broad story is similar: bromazolam is usually found with other drugs rather than on its own.

In UK data, cocaine, diazepam, gabapentinoids, and other depressants often appear alongside it. Unlike the US datasets, fentanyl is not usually dominant in the UK context, which is not surprising given how different the opioid markets are.

So the polydrug pattern is similar, but the specific co-detected drugs reflect the local drug market.

Exactly.

So let's move on to the second paper, which looks at a related but different compound: desalkylgidazepam.

Why don't you introduce that one, Rebecca?

Desalkylgidazepam is a metabolite of gidazepam.

So what is gidazepam?

Gidazepam is a benzodiazepine that has been used medically in some Eastern European countries and the former Soviet sphere. It has been used for anxiety and related indications, but it is not a standard prescribed benzodiazepine in places like the UK or Canada.

Desalkylgidazepam is one of its metabolites, but importantly it has also appeared as a drug in its own right.

So this paper looked at desalkylgidazepam detections in British Columbia. It was first detected there in the drug supply in April 2022, so it is relatively new.

Why don't you take us through some of the figures?

The paper looked at 63 post-mortem blood cases where desalkylgidazepam was detected between April and December 2022.

Around 77 percent of the cases were men, with an average age of about 45. So again, not wildly different from the bromazolam demographics.

The mean concentration of desalkylgidazepam was about 42.2 nanograms per millilitre, with a median of 24.5 nanograms per millilitre.

And, once again, there was heavy polydrug use. Fentanyl was present in the overwhelming majority of cases. Caffeine, methamphetamine, amphetamine, and bromazolam also appeared commonly.

So the overall picture is very similar to the bromazolam paper: another novel or unusual benzodiazepine, showing up mainly in heavily polydrug deaths rather than isolated single-drug cases.

Exactly.

Do we know much about how desalkylgidazepam compares pharmacologically to gidazepam or to more familiar benzos?

There are some data suggesting that desalkylgidazepam has much higher affinity for the GABA-A receptor than its parent compound gidazepam, which is quite interesting because it suggests the metabolite may actually be more pharmacologically relevant than the parent.

It also appears to have a fairly long half-life, on the order of around 80 hours or so, which means it hangs around for quite a long time.

So if someone takes a dose of it, substantial levels may still be present days later.

And in the British Columbia paper, about 96.8 percent of cases had fentanyl co-detected, which is even higher than in the bromazolam dataset.

Do we know whether it is being sold as itself, mixed into opioids, or passed off as other benzodiazepines?

I suspect it is probably a bit of all three, but certainly there are signs that it appears in counterfeit benzodiazepine tablets and mixed-drug supplies.

We checked WEDINOS in the UK as well, and it does appear to have shown up in UK drug checking data, often in tablets or samples that people believed were other benzodiazepines.

So it is definitely one to keep an eye on.

And as you said earlier, bromazolam has hung around longer than some other novel benzos, which makes me wonder whether desalkylgidazepam or other related compounds might become more prominent as controls tighten on existing ones.

That is exactly what I was thinking.

So what is the main take-home from these papers?

Novel benzodiazepines are now a routine part of post-mortem toxicology in some places. They are often not present alone, they are usually found with opioids, stimulants, alcohol, or other sedatives, and that makes interpretation difficult.

Analytically, they are also a problem because the drug market keeps changing. You can think you are testing for all the important benzos, and then a new one appears that is not yet in your library or does not cross-react properly in the initial screening method.

That is especially true if you are relying on broad immunoassay screening. A negative benzodiazepine screen does not necessarily mean no benzodiazepine is present if the assay does not cross-react well with a particular novel compound.

Although, in fairness, some of the novel benzos do still trigger a benzodiazepine screen and at least give you a clue that something is there.

Yes. The screen may not tell you which one it is, but it may still point you in the right direction.

So I think the broader message is that this is an evolving area and there are real analytical and interpretive challenges that come with that.

Exactly.

I think we should wrap it up there. Thank you everybody for listening.

Do give us a like and a follow if you haven't already. We really do appreciate it.

And do drop us comments as well. You can follow us on Instagram at @the_tox_lab.

Feel free to send us messages if you've got paper recommendations or things you'd like us to cover.

Hope you all have a great week. Bye.