THE TOX LAB

Podcast Transcript

Episode 1: Nitazene and Xylazine

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TRANSCRIPT

Welcome to The Tox Lab. I'm Rebecca.

I'm Rob. Today we're going to be talking about nitazenes and xylazine.

Let's start with the recent OHID report on deaths linked to potent synthetic opioids in the UK.

For anyone who has not come across it, OHID is the Office for Health Improvement and Disparities, the body that succeeded parts of Public Health England. They have been looking closely at the recent emergence of novel opioids in the UK.

And nitazenes are the big concern in that space at the moment.

Exactly. Nitazenes are a class of very potent synthetic opioids. They were first synthesised in the 1950s during research into alternative analgesics, but they were never adopted clinically because they offered no clear advantage over existing opioids and carried significant risks.

Then, from around 2019 onwards, they began to re-emerge in illicit markets. At first they were mostly niche research-chemical compounds, but more recently they have appeared in much more mainstream drug supplies, especially mixed into heroin or sold in tablets that are marketed as benzodiazepines or other medicines.

So what did the OHID report say?

The report covered the period from 1 June 2023 to 31 May 2024 and recorded 179 confirmed deaths involving novel synthetic opioids in the UK, mostly nitazenes.

Which is a substantial number.

It is. If you compare that with the broader background of drug-related deaths, it is a meaningful proportion, and the report also makes it clear that this is likely to be an underestimate rather than a complete count.

Yes, because case ascertainment is difficult, testing is variable, and not every lab is necessarily looking for the full range of nitazenes.

Exactly. So the confirmed number is almost certainly lower than the true number.

One thing that stood out to me was the regional distribution. Some areas had quite low counts, including the North East, which seemed surprising.

It did, although that may reflect differences in local supply, case detection, testing practice, or reporting completeness. Regional comparisons are interesting, but they need to be interpreted cautiously.

What about the breakdown by compound?

That was one of the more useful parts of the report. Protonitazene appeared to be the most prevalent, followed by compounds such as isotonitazene, metonitazene, and others that fit broadly with what we have been seeing in practice.

So the report is reassuring in one sense, because it suggests there is not some completely unexpected nitazene analogue dominating nationally without anyone noticing.

Yes, although it also highlights how dynamic this class is. Nitazenes are not one drug. They are a family of related compounds, and different members of that family can vary in potency, prevalence, and the way they appear in toxicology casework.

That is a really important point. People sometimes talk about "nitazene" as though it is a single substance, but it is not. These are distinct chemicals that share a common scaffold and broadly similar opioid effects.

The report also included cases where the specific nitazene was not identified, which is interesting.

Yes, there were a number of unspecified nitazene detections. My suspicion is that some of those arise because certain pairs of compounds are analytically difficult to distinguish if a lab is relying mainly on mass spectrometry without strong chromatographic separation.

For example, protonitazene and isotonitazene have the same molecular formula and can produce very similar fragmentation patterns, so if the retention time data are not strong enough, a lab may be reluctant to call one rather than the other.

That seems like the most likely explanation.

It does to me as well, although without laboratory-by-laboratory detail we cannot be certain.

Another thing I would have liked in the report is more detail on what the nitazenes were actually mixed with in fatal cases.

Yes. Were they mainly in heroin? Were they mainly in counterfeit benzodiazepines? Were they present in fake oxycodone tablets? That kind of breakdown would be extremely helpful.

We do have some clues from WEDINOS, though.

We do. WEDINOS is the Welsh Emerging Drugs and Identification of Novel Substances service. It is a drug-checking and harm-reduction service where people can submit samples for analysis.

Their published results have shown nitazenes appearing in a range of products, including powders sold as heroin, tablets sold as diazepam, and even pills sold as oxycodone.

And that is deeply worrying, because it means people may think they are taking one class of drug when in fact they are taking a very potent opioid.

Exactly. We have also seen fake blister-packed tablets that look convincingly pharmaceutical but contain nitazenes, bromazolam, or mixtures of both.

Which brings us neatly to bromazolam. That is another compound turning up quite often alongside nitazenes.

Yes. Bromazolam is a designer benzodiazepine. It was never approved for clinical use, but it has become very common in the illicit market over the last few years. It causes the sort of effects you would expect from a benzodiazepine: sedation, amnesia, impaired coordination, and, when combined with opioids, increased risk of severe respiratory depression.

And unlike some novel benzodiazepines that appear briefly and disappear, bromazolam has proved quite persistent in the market.

It really has. It has been around longer than many people initially expected, and users do seem to recognise it as a distinct product.

So the overall nitazene picture is that we have a group of very potent opioids, increasingly found in counterfeit and contaminated drug supplies, with incomplete but clearly significant mortality data.

That is exactly how I would summarise it.

Let's switch to xylazine.

Xylazine is a veterinary sedative and tranquilliser. Pharmacologically it is an alpha-2 adrenergic agonist, so it does not work like an opioid, but it can produce sedation, hypotension, and other depressive effects. In the United States it has become very common as an adulterant in the illicit opioid supply.

And over the last year or so it has started to emerge in the UK too.

Yes. It is still much more established in North America, but it is now relevant enough here that toxicologists and clinicians need to know about it.

The first paper we looked at was a study of emergency department patients with opioid overdose, comparing those who were xylazine-positive with those who were opioid-positive without xylazine.

What was the design?

It was a multicentre prospective cohort study. They included 321 patients who presented with confirmed opioid overdose. Ninety of them were positive for both an opioid and xylazine, and 231 were positive for an opioid without xylazine.

And they looked at outcomes such as naloxone administration, cardiovascular and neurological features, intubation, CPR, and death.

Exactly.

What was surprising was that there was not a dramatic difference between the groups.

No. In fact, the only clearly statistically significant difference they highlighted was that the xylazine-positive group received CPR less often than the opioid-only group.

Which feels counterintuitive, because the usual assumption is that xylazine worsens opioid toxicity.

Yes, and there are a few possible explanations. One is that the study only includes patients who made it to hospital. If the sickest xylazine-associated overdoses resulted in pre-hospital death, those cases would not be captured.

So the xylazine-positive group in the study may not represent the full severity of xylazine-associated poisoning.

Exactly. Another issue is that the study did not deeply quantify the opioid burden in a way that fully answers whether the xylazine group had less opioid exposure overall. That makes interpretation difficult.

And xylazine itself may be underestimated analytically, because it can occur at quite low concentrations and it has a relatively short half-life.

Yes. So this study is interesting, but I would not take it as evidence that xylazine is harmless or protective. I think it mainly shows how messy real-world overdose data can be.

I agree.

The second xylazine paper was a very different kind of study.

Yes. That one was an animal pharmacology paper looking at withdrawal and receptor interactions in mice exposed to fentanyl, xylazine, or both.

So this is much more mechanistic.

Exactly. The authors dosed male and female mice with fentanyl, xylazine, or the combination, then precipitated withdrawal using naloxone or an alpha-2 antagonist and looked at behavioural signs of withdrawal.

One of the interesting findings was a sex difference. In female mice, xylazine withdrawal seemed more prominent than in males, and the combination of fentanyl plus xylazine produced particularly marked effects.

Yes, and the mechanism behind that was not entirely clear, but it suggests that we may not fully understand the dependence profile of xylazine.

Which matters, because if xylazine is becoming embedded in opioid supplies, then withdrawal management may become more complicated than simple opioid withdrawal alone.

Absolutely.

The paper also included receptor-binding work.

It did. As expected, xylazine showed activity at alpha-2 adrenergic receptors, but there were also signals suggesting interactions at other receptor systems, including kappa opioid receptors and serotonin-related targets.

Which raises the possibility that xylazine is pharmacologically more complicated than the simple shorthand of "veterinary sedative mixed with opioids" might suggest.

Yes. That shorthand is useful, but it may not capture the full story.

We also talked about xylazine-associated skin lesions, which are well recognised in the US. The mechanism is still debated, but vasoconstriction and local tissue injury may both be relevant.

And those lesions can be severe.

Very severe.

So what is the take-home message from the xylazine discussion?

For me, it is that xylazine is clearly important, but we still do not fully understand how it modifies opioid toxicity, how often it changes outcomes in practice, or exactly how dependence and withdrawal work when it is used chronically alongside opioids.

I would say the same. The emergency department data do not give a simple answer, and the animal pharmacology data show that the biology is more complex than people may assume.

And taken together with the nitazene issue, it means the illicit opioid supply is becoming more chemically unpredictable and therefore more dangerous.

Exactly.

Any final thoughts before we wrap up?

Only that there seems to be a growing literature on both nitazenes and xylazine, so I suspect we will be revisiting both topics again soon.

Definitely. Thanks for listening, everyone, and we will see you next time.