THE TOX LAB

Podcast Transcript

Episode 33: Tianeptine - From Antidepressant to Gas Station Heroin

This transcript was created by AI from audio and lightly edited for readability. Treat it with caution, and assume occasional transcription errors may remain.

TRANSCRIPT

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be looking at tianeptine, or as it's commonly known, gas station heroin.

I was thinking, Rebecca, in general, other than petrol, is there ever anything good to buy in a petrol station? I mean, if you've got one with a little M&S shop and you've got a Percy Pig's. OK. All right.

I was thinking, in general, flowers from a petrol station. Bit sad. Sad, and you've either forgotten a birthday, forgotten an anniversary, or you need to apologise for something. Yeah, they're not good.

Sandwiches from a petrol station, in general, maybe not great. Bit dodge. So imagine going to the petrol station and buying drugs. It's just weird.

And yet that is what is happening in some parts of America. We've done a bit of a series, haven't we? We've talked a bit about hydroxymitragynine recently, and we talked about delta-8 THC. And tianeptine is sort of similar, actually.

It's falling into that legal grey zone in the States. But it's got a bit of a history, hasn't it? Let's look a bit at the history and talk a bit about what tianeptine is. Before we jump into today's episode, if you want to stay up to date on our content or want to get in touch with us, you can find us on Instagram at @the_tox_lab.

We also have a LinkedIn page. And if you don't use socials, but still want to get in contact, you can email us at thetoxlab@gmail.com. So what is tianeptine and what is its history? It was first synthesised in the 1960s.

It was a French pharmaceutical company, which I'm not going to try and pronounce. And it was at a time where there was a lot of new compounds being developed. In terms of its structure, it's very similar to tricyclic antidepressants, things like amitriptyline. And so this drug was synthesised.

It had a tricyclic structure and it was shown to have antidepressant properties. Therefore, it was considered to be a tricyclic antidepressant. But some early research looked at its receptor effects. And unlike tricyclic antidepressants, which tend to act as serotonin and noradrenaline reuptake inhibitors, this drug seemed to enhance the reuptake of serotonin, which was counterintuitive at the time.

And so it was presumed it had antidepressant activities through this novel mechanism. Fast forward a few years later and more research had been carried out and it was shown that it actually had opioid properties. It actually acted on the mu opioid receptor and to some extent the delta opioid receptor as well. The mu opioid receptor is the receptor that is responsible for most of the effects that we think of when we think of opioid effects.

But the delta opioid receptor also has some roles in mood regulation and things like that. But interestingly, tianeptine also was later discovered to have an effect through the glutamate pathway. We talked a few

weeks ago about ketamine and how ketamine has an antidepressant effect by acting on this glutamate pathway. And this leads to increased neuroplasticity.

And so it's thought now that tianeptine's antidepressant activities are actually through both mu opioid receptor activity and glutamate activity. And therefore it's not a traditional antidepressant in that sense at all. It was just coincidence that it happened to have a similar structure to other antidepressants and led to antidepressant activities. So in terms of its use globally, quite a few countries do use tianeptine as an antidepressant.

It's prescribed in France in particular, where it was first discovered. They have moved to have stricter controls on it, but it is still legal to use as a medicine. Some countries have never approved it for therapeutic use. So the UK, the US, there's no FDA approval in the US for tianeptine.

But it has been emerging increasingly in what are sold as food supplements. It's sold as a food supplement or a wellness elixir. And as we were saying, can be purchased at petrol stations or gas stations. So this week, we're going to be looking at three papers looking at tianeptine, a clinical toxicology case, some poison control data, and a rather surprising outbreak involving tianeptine a bit later on, which I don't want to spoil.

So Rebecca, let's jump in and let's look at this first case. So between 2014 and 2017, there was a statistically significant increase in calls to poison centers related to exposure and intentional abuse of tianeptine in supplements. Between 2014 and 2020, discussions on social media sites about benefits decreased and there was more chatter about negative consequences and withdrawal effects. Tianeptine has been used as a replacement or to alleviate withdrawal symptoms from other substances, to self-medicate psychiatric issues, or to enhance quality of life, mood, or performance.

And co-ingestion with other substances can potentiate the effects of tianeptine. Such substances include phenibut, ethanol, benzos, and opioids. So the clinical case we're going to talk about involves a 67-year-old Caucasian male with significant polysubstance misuse history, chronic hyponatremia, major depressive disorder, and anxiety. He was brought to the emergency department by ambulance for lightheadedness and lethargy after stopping over-the-counter supplements containing tianeptine. He started taking them to get high about four weeks prior to his admission and he was taking four to eight capsules a day purchased from his local smoke shop.

And the last dose he took was about 12 hours prior to his admission. He described the withdrawal from these supplements as being unbearable and described suffering from constipation, urinary retention, chest pain, shortness of breath, palpitations, headache, blurred vision, fevers, chills, and anorexia. So quite a range of symptoms he was describing there, although on a complex medical background as well. He was also on many prescription medications, including clopidogrel, Xanax.

He was on some diuretics as well. And Xanax in this case was actually prescribed. Yes. In the UK, obviously, when we see Xanax, we're often thinking street benzos, but actually in the US it is prescribed.

On his admission, his vitals were stable, but he did have dilated pupils. He remained alert and orientated, but had a loss of gross motor strength. And he was given medication for nausea and vomiting and normal saline. So his ECG on admission showed a prolonged QRS complex.

The urine drug screen was positive for benzodiazepines and he did have hyponatremia, which was thought to be caused by his ACE inhibitor and his angiotensin-2 receptor antagonist. What was interesting is they never confirmed the use of tianeptine and never sent the sample for specialist toxicology testing. So whether or not there was tianeptine at play is potentially still up for debate. And he did make a full recovery.

He was given alprazolam to treat his agitation and he was given sodium bicarbonate to reduce his QRS complex, but this never fully corrected and in the paper they hypothesized that this was caused by the hyponatremia and his other medications, so it wouldn't have been fully resolved. In some respects, this is quite a messy case, isn't it, with a lot going on? But also it's quite a good example of real life because in real life poisoning and withdrawal cases are not always textbook. It's interesting, isn't it, how quickly he developed withdrawal.

Twelve hours after stopping, he was describing, some of those were classical opioid withdrawal symptoms. Some of them weren't, right? Some things are more associated with opioid use rather than opioid withdrawal. And he had quite a complex history of significant polysubstance use, so the fact he's described this withdrawal as being unbearable does say something.

That's fair, so he's probably gone through similar withdrawals on other drugs and yet described this as quite significant. When we look at the pharmacology, it's both an opioid and a drug that acts like ketamine. Opioid withdrawal, generally considered unpleasant. Ketamine withdrawal, generally considered unpleasant.

Is this mega-withdrawal? Potentially. The other thing to remember with this case is we've got no information on the dose that he was taking. We know he was taking four to eight capsules a day, but we don't know how much tianeptine was present within those capsules or what other substances could have been present.

Yeah, that's completely fair. The lack of toxicology in this case clouds things a bit, although I've no idea what detection windows are like for these things. Actually, if he was undergoing withdrawal, we could well be missing things if we had done tox depending on how quickly they're cleared. So an interesting single case presentation, hard really I think to unpick some of that, although it does suggest withdrawal is a real thing from tianeptine, doesn't it?

So let's now move on to the poison control data. So this next paper looks at data from the National Poison Data System and it's covering single substance exposures between January the 1st, 2015 and December the 31st, 2023. Across this data set there were 892 exposures to tianeptine, which is about 99 per year. 37% occurred in individuals aged between 30 and 39, 22% between individuals aged 20 and 29 and 20% in individuals aged between 40 and 49.

The majority of these were males and 92% of all exposures occurred at residences. So quite a range of ages, not one particular age group seeming over-represented or anything like that. The majority of these exposures that were reported were acute exposures followed by chronic exposures and then what they classed as acute on chronic exposures. The majority of these were intentional, 40% were attributed to abuse and more than a fifth of exposures were associated with withdrawal.

I think that's something we haven't quite touched on actually but probably should mention. The opioid-like effects of tianeptine occur at dosages much higher than those described as therapeutic for antidepressant effects. So more than 50% of all abuse-related exposures were associated with moderate effects, 15% were associated with major effects and 25% of abuse-related exposures required someone to be admitted to critical care. Quite a chunk then were really quite severe.

In a withdrawal setting, 49% of individuals experienced moderate effects, 32% experienced minor effects and 4% experienced major effects. I think it's really hard to interpret this sort of data without having a good feel for what counts as minor versus moderate versus severe. If you quantify it by saying they were admitted to critical care, I can understand that. So 60% of individuals in this group were treated and released, 16% of which ended up in critical care and almost half of them required a medical admission.

They also split this data up geographically, so Southern US were responsible for 67% of all exposure calls, followed by the Midwest at 14%, the West at 10%, and Northeast at 9%. And Alabama was responsible for 24% of all exposures, followed by Mississippi. So 24% of the entire data set all occurring in one state? Yep.

So exposures have shown a non-linear increase, going from about 17% in 2015 to 250% in 2023. Comparing the four-year periods from 2015 to 2018 and 2020 to 2023, exposures increased by 200%. So clearly on the increase? Looking more into clinical effects, in situations where it was being abused, agitation was the most frequent clinical effect, affecting 34%, followed by tachycardia, confusion, hypertension, moderate CNS depression, respiratory depression, and other effects such as bradycardia, acidosis, seizures, and coma.

In withdrawal situations, agitation was again the most frequent clinical effect, affecting 55% of individuals, followed by nausea, tachycardia, vomiting, hypertension, and seizures. In terms of treatment, IV fluids and benzodiazepines were often the most common choice. Naloxone was given in 18% of cases. Again, it's

quite a range of symptoms, isn't it?

It's not behaving like a classical opioid in terms of the effects that people are describing. And other treatments included mechanical ventilation, vasopressors, anticonvulsants, and cardiopulmonary resuscitation, depending on the severity of the effect seen. So it is important to remember with this data set that not all data within the study period was reported to poison control. And the same person may appear in the data set multiple times from different exposures.

So this is clearly a real and increasing phenomenon. Some effects are quite severe, severe enough to cause hospitalization. And even if these all resolve with no long-term ill effects, it's still quite a burden on healthcare, because a lot of these people were being taken to hospital.

I just find it so bizarre that these were bought at petrol stations. Now, there have been some shifts in control, haven't there, since this poison control data came out. Some states have controlled tianeptine, Mississippi included. Although not all, it's only a few.

I think the range of effects people were describing as well really shows how complex its pharmacology is. I think that probably can make it unpredictable to users as well. Yeah, definitely. It seems to be such varied negative effects associated with it that I don't think anyone can predict what's going to happen if you do take it.

And especially what withdrawal is going to be like as well. So let's look at our final paper. So this last paper focuses on tianeptine products and exposures in the state of New Jersey. So the New Jersey poison information education system were typically receiving less than two calls a year related to tianeptine.

But between June 2023 and February 2024, they received 41 calls regarding exposure of people becoming ill shortly after consuming products containing tianeptine. And this is a much bigger increase, isn't it, compared to what we were just looking at? Yeah. So these 41 calls were reported from 22 individual hospitals.

37 individuals experienced acute effects after ingesting tianeptine-containing products. Two were chronic users and two were suffering from withdrawal. So this averaged 4.6 cases being reported per month. And in the 10 months after this period, the number of calls dropped to 0.8 per month.

So there's something a bit strange going on during this period. There was a clear spike. Yeah. So of the 37 individuals with acute effects, 34 of these were unique patients.

They ranged between the ages of 19 and 64 and the majority of them were male. An overwhelming 97% of these described having altered mental status. Fifty-seven percent of them had tachycardia, and hypotension, seizures, and respiratory depression were also common effects. One individual went into cardiac arrest but no fatalities were reported.

84% of these involved people purchasing Neptune's Fix elixir from gas stations, smoke shops and convenience stores. And nine out of the 37 presentations involved co-exposures, and kratom or mitragynine was the most frequently reported. For treatment benzodiazepines were given in 54%, naloxone was given in 32%, of which two patients responded, three didn't and seven were inconclusive.

So the effects of these acute exposures were quite severe. 16 people were intubated, 24 were admitted to the ICU. So quite severe adverse effects. Quite a lot of overlap with what we saw in the last data set though, right?

Yeah, so from two of these patients in this data set they were able to obtain six bottles of Neptune's Fix elixir to test. So ingredients listed on these included tianeptine, kava, magnesium, a variety of different solvents and flavourings. So four of them were cherry flavoured and two of them were tropical. Once again, marketing aimed at children.

Yeah, a little bit. So these were sent to the CFSRE for testing. They used both GC-MS and LC-QTOF-MS. So five of these bottles were open.

One of them was completely sealed. All of them contained tianeptine. But there were some other substances present that you might not expect. And these included THC, CBD, MDMB-4en-PINACA and ADB-4en-PINACA.

And these were found in both the open and the sealed bottle as well. So THC and CBD, compounds found in cannabis plants, and MDMB-4en-PINACA and ADB-4en-PINACA, both synthetic cannabinoids. None of which were listed on the ingredients label. So they also managed to test blood samples from two of the patients.

And in the first one, tianeptine was found at a concentration of 460 nanograms per millilitre. And the quoted therapeutic range is between 278 and 366 nanograms per millilitre. And MDMB-4en-PINACA was also detected. In the second individual, only tianeptine was present at a concentration of 89 nanograms per millilitre.

That possibly represents a longer period after exposure, doesn't it? And therefore, detection or lack of detection of the synthetic cannabinoid doesn't rule out that it may have been there. In the two individuals who presented with withdrawal, they were on quite a large daily dose of tianeptine. One was on seven grams a day, and one was on 13.5 grams a day.

And the standard doses to treat depression are between 25 and 50 milligrams per day. So huge doses. Huge doses. So one individual self-tapered to a lower daily dose and was admitted for inpatient detox.

And one individual abruptly stopped and experienced withdrawal, consistent with opioid withdrawal, and experienced symptoms like vomiting, diarrhoea and dilated pupils. Symptoms did improve with buprenorphine, clonidine, and lorazepam. So I think this outbreak is really quite shocking, isn't it?

Although, I guess, in retrospect, if you're buying drugs at a petrol station, maybe we shouldn't be surprised. But something that's being marketed as an elixir with an ingredients list, clearly having other drugs in it on top of what it's supposed to contain. And I guess it does call into question that much larger poison control data set, whether any of those individuals, although there were supposedly single substance exposures, whether there were other drugs in there that could have been interacting and causing the wide variety of symptoms that were reported. I was thinking that too, actually.

Potentially synthetic cannabinoids could have accounted for some of that weirdness. I want to drill a little bit into the kava present. We've never talked about this on the podcast, although I think maybe there'll be an episode coming on. Kava has effects somewhat similar to benzodiazepines.

I wonder how that, if at all, factored into any of this. So all in all, it's a really weird drug, isn't it? It was marketed originally as an antidepressant. In this context, it seems to be behaving much more like an opioid.

Do we need to stop calling it an antidepressant? Do we need to think about it more on a basis of its opioid effect? I mean, I guess this is a bigger question of how we classify drugs, isn't it? Yeah, definitely.

Just because it looks like a tricyclic antidepressant doesn't make it one. Very true. We haven't talked much about the metabolism of tianeptine. But similar to mitragynine, when we were talking about that a few weeks ago, it does have a metabolite that's a lot more active at the opioid receptor.

And so it's possible some of these effects are mediated by its metabolite. It's got a really boring name, MC5. That is really boring. But it is possible, actually, that this is responsible for some of the effects.

And that's perhaps not being truly picked up on toxicology and things like that. These aren't really messy cases, aren't they? Yeah. Both the original case and the poison control data set, a large amount going on in terms of this bizarre toxidrome that doesn't seem to resemble any one drug.

I mean, I feel like these cases and this drug in particular highlight sort of the scary world of food supplements and things like that. Because it's being marketed as a supplement in some cases. And it's not being regulated in the way I think people necessarily believe it is. So you've got no idea what's going into it.

That's a concern, isn't it? You get a bottle. It's got ingredients on the side. It calls itself an elixir.

It's being sold at a completely legitimate business. The assumption is this is fine. Yeah. And actually, that might not be the reality.

I do think it's a really interesting regulatory world. It contrasts quite a bit from the UK, doesn't it? Because we do now have the novel psychoactive substances act. Before that, there were head shops selling all sorts of unregulated compounds.

And while some of that still exists, probably behind closed doors, we certainly don't have the open sale of drugs under the guise of legal highs that we used to have. But I think the food supplement area is a really interesting one, because some things are marketed as food and therefore seem to fall through this legislation a little bit. So obviously, all of these studies and papers came out of the US where tianeptine is currently in a bit of a regulatory minefield and sold openly. And France legally prescribes this, although it did reclassify it as a more controlled prescription drug due to its opioid effects.

What do we think about the UK? Is tianeptine out there and not being picked up? Do we think we're going to see similar occurring in the UK? I mean, like with a lot of the drugs we've talked about in recent weeks, where they're more predominant in the US, it'd be interesting to see if the pattern does get mirrored over here.

It's definitely one to have on the radar, isn't it? Definitely. I do wonder how different the UK would have been in the absence of the novel psychoactive substances act, whether this might have been the direction of travel and we might have seen things like tianeptine being sold openly. It's definitely quite likely.

So in summary then, tianeptine is a thing. It's a really interesting compound with a rich history. It's got some really, really interesting pharmacology. But I do find the idea of being able to buy it as a drug at a petrol station quite strange and clearly there seems to be some negative effects.

And so I guess the moral of the story is don't buy flowers from the petrol station, don't buy sandwiches from the petrol station and don't buy drugs from the petrol station. All good advice. I hope you've enjoyed listening to us this week. If you've enjoyed listening, do like the podcast and follow the podcast.

That would be really, really helpful. We do appreciate you all coming back to listen. Hope you will have an amazing week and we'll see you next time. Bye!