The Tox Lab

Episode Transcript

Episode 75: Kratom Is Changing - New Semi-Synthetic Compounds & Rising Harm

Edited transcript

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Clean Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking another look at Mitragynine.

Now Mitragynine was an episode we covered episode 25 I think. Yeah. And it was almost to the day a year ago, which is I think quite incredible. It's a bit mental when you think about it that it was that long ago.

It's our second most popular episode which I'm very proud of. Yeah. Uh it's definitely been a very popular episode and we've had quite a few people reach out to us and really ask for an update as to what's going on the mitragynine scene. What else has happened in the last year, Rebecca?

Top three highlights the last 12 months. I mean, we celebrated a year on the podcast, which felt very impressive. We're coming up to a year and a half now. We now have our studio.

So that's also quite exciting. That is exciting. Also been very lucky and had a load of our papers published. That is very true as well.

So all in all, it's been a good 12 months. A lot has happened. A lot has happened on the mitragynine scene. A [clears throat] year ago, we gave an intro to mitragynine and kratom and what it was.

And what was occurring at the time was really a warning about the move towards semi-synthetic compounds. I'm not going to repeat all of the background and if you haven't go and listen to that episode because it really does intro where we are now quite well. In essence, kratom is a plant from parts of Indonesia and Malaysia. It contains compounds called mitragynine alkaloids and there is a trend towards taking that mitragynine and chemically altering it and producing drug compounds which are based on that original mitragynine compound.

The most popular one at the moment is 7-hydroxymitragynine that does occur naturally in mitragynine very low concentrations and it also occurs as a metabolite of mitragynine but what we are seeing is we are seeing drug products where that is the primary compound found and a year ago the FDA issued a warning didn't they saying these compounds do pose a risk and there has been some back and forth over the legislation and control of these compounds and here we are 12 months later. 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 on 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 our episodes, you can email us at thetoxlab@gmail.com. So the first paper this week is actually a report published by the CDC on their morbidity and mortality weekly report and this was looking at calls to poison centers relating to kratom and mitragynine. So this report covers exposure report data from the national poison data system which collects data from 53 different poison centers and it covers from the 1st of January 2015 to the 31st of December 2025.

They included both single substance and multi-substance exposures. And during this time period, there were 14,449 kratom exposures that were documented with 3,434 of the exposures occurring in 2025, which represented a 1,200% increase compared to 2015 where 258 exposures were reported. And it was really that key spike, wasn't it? That big.

It's hard to describe, but there was a massive spike on the graph. Yeah. And there has clearly been something within the last 12 months that has led to a really huge rise in calls to poison centers related to kratom and kratom alkaloids. And one of the reasons for this could be the rise in these semi-synthetic mitragynine compounds.

7-hydroxymitragynine which is more potent than traditional mitragynine. You've got mitragynine pseudoindoxyl and that's even more potent than 7-hydroxymitragynine. And there's also dihydro-7-hydroxymitragynine also known as MGM15. And so these compounds are starting to emerge in popularity.

They're occurring in smoke shops sometimes gas stations I believe. And unlike traditional mitragynine found in kratom, they're a lot more potent and it's believed that they carry a lot more risk. And certainly this recent spike in poison center data may not be but could be caused by this rapid proliferation of these novel semi-synthetic compounds. Now what is interesting is I was doing some digging on the internet just this morning to look at the availability of these compounds and I think the marketing is really quite unclear because as we know is a naturally occurring product.

Some of these semi-synthetic compounds are marketed as naturally occurring products and that's not the case. Although some of them do occur in nature in lower concentrations, particularly the 7-hydroxy, this form that they're presented in here is clearly not natural. And at least one website, which was selling MGM15 and claiming to be selling these natural tablets, next to it was actually selling a novel opioid compound. Oh, that's terrifying.

So, the way these compounds are marketed really is quite misleading. And we do need to look a bit at the potency. As I've said, they're really quite potent. And unlike mitragynine, which seems to have a bit of a ceiling effect, and we explored this in our last episode, these compounds don't seem to have that.

The maximum effect by mitragynine seems to be limited by the body's ability to convert it to 7-hydroxy, whereas these compounds are potent in their own right. So, there really is quite a lot of concern that these compounds could be contributing. And actually they seem to be seeing a real rise in proliferation. So looking back at the poison center data, multiple substance exposure reports accounted for 38% of all associated exposure reports and the annual rates of multiple substance exposure reports exceeded the rate of the single substance exposure reports.

The most common substances involved in co-exposures were ethanol in 22%, opioids in 16%, benzodiazepines in 15%, anti-depressants in 14%, cannabis and cannabinoids in 12% and stimulants in 11%. Males on average accounted for the highest percentage of kratom associated exposures. And in addition to exposures increasing, hospitalizations also increased during the study period by 1,200% for single substance exposures. In 2015, there were 43 hospitalizations, but there were 538 in 2025.

And that is a massive increase, right? Yeah. And this increase is mirrored in the multiple substance exposures. And this increased by 1,300% from 40 in 2015 to 549 in 2025.

But presumably given that they both seem to be mirroring one another, the issue here wasn't other substances. The issue here was the mitragynine. Right. It seems to be.

Yeah. 233 deaths associated with were reported during this period with 79% involving multiple substances and 62% of the fatalities involving opioids. And I think your stat there actually does hit the nail on the head quite well as well, doesn't it? One of the criticisms of extended control of kratom is that people who support it say well it doesn't tend to lead to fatality and actually this data does kind of suggest that it's one of those where it doesn't on its own often more often in a poly substance setting and that is I think reflected in the stats.

One of the questions we were asked by one of our listeners actually was whether this phenomenon is occurring outside of the US because a big thing in the US. It's not something that we tend to see a lot of in the UK for example. So according to the UNODC early warning advisory data 58 countries in total have reported with 30 countries reporting in 2024 in 2025 and one so far in 2026. In 2025, kratom was reported in Austria, Belgium, Brunei, Canada, China, Malaysia, Singapore, Spain, Tanzania, Thailand, Turkey, Ukraine, the UK, and the US.

7-hydroxymitragynine was reported in five countries in 2025, including Australia, Canada, the Ukraine, US, and Germany. And when looking at mitragynine pseudoindoxyl, this was only reported in the US in 2025. So it does look like other countries are starting to see particularly the 7-hydroxy but it does seem to be quite local really to the US. So we want to look a little bit deeper now into one of the newer compounds.

We've talked about hydroxy mitragynine. One of the other compounds as I've mentioned it already is tragenine pseudoindoxyl and this compound is thought to be even more potent than 7-hydroxy. We found a single clinical case report looking at an individual who was exposed to mitragynine pseudoindoxyl. So this case involves a 34 year old male with a history of depression who presented to the emergency department with suicidal ideation and depressive symptoms and was admitted to an inpatient psychiatric unit.

He reported remission from opioid use disorder for the last 6 years and urine toxicology testing did not detect the presence of any opioids. Despite this, he was experiencing chills, cold flashes, restlessness, diaphoresis, mild body aches, and nausea, which progressed over the next two hours to develop severe body aches, tremors, pronounced restlessness, vomiting, and diarrhea. And this is classic opioid withdrawal syndrome, right? He had a blood pressure of 168 over 107 and a heart rate of 115.

The patient did report regular consumption and mentioned that similar withdrawal symptoms occurred at home if his dosing exceeded 5 or 6 hours and he had last used 7 hours before his presentation. When looking at his history, he initially started using kratom 5 years previously and a year ago progressed to using 7-hydroxymitragynine which he perceived as more potent in terms of euphoria and mood effects. His dose continued to increase from two 15 milligram tablets a day to 65 milligrams four to six times a day resulting in mild chills and discomfort upon awakening when his dose was delayed.

Three months before his admission, he started taking mitragynine pseudoindoxyl taking two 8 milligram tablets as he found these were more potent than 7-hydroxymitragynine and again his dosing increased to 20 milligram doses approximately nine times in 24 hours which cause financial strain and marital stress decreased productivity lethargy and disengagement at home and this dose escalation is quite significant isn't it as we've said the order of potency really is mitragynine 7-hydroxymitragynine and then pseudoindoxyl and the dose he taking by the end of pseudoindoxyl was quite significant when you scale that up back to standard mitragynine doses.

We're talking what possibly hundreds of milligrams of mitragynine equivalent and he was dosing throughout the night as well because he couldn't bear the withdrawal effects when he wasn't taking it during the night. And actually I think that dose escalation in the context of more potent compounds is something we don't talk about enough actually. I've seen a case of an individual who was taking what he thought was oxycodone or originally he was taking oxycodone and his supply changed from being genuine oxycodone to nitazenes and the increase in potency of his supply led to this real dose escalation.

Whenever he attempted to reduce his dose he described extreme discomfort including feeling like he was crawling out of his skin but he had expressed wanting to come off of it. He had a clinical opiate withdrawal scale score of 31 and was treated with supportive and symptomatic measures including clonidine, hydroxyzine for anxiety, loperamide as needed, Compazine for nausea and gabapentin. His symptoms peaked over the first 24 hours and gradually improved over 72 to 96 hours. By day two, his clinical opiate withdrawal score had reduced to 10 and this had reduced again to eight by day three and by day five, the patient was symptom free.

Fluoxetine was prescribed based on the symptoms of depression he had experienced and he was started on naltrexone therapy and was referred to outpatient addiction services for ongoing monitoring and support. Two weeks after his admission, he ingested three 20 milligram mitragynine pseudoindoxyl tablets after a stressful event and reported fatigue but no euphoria. At his follow-up a month later, he remained abstinent from the mitragynine pseudoindoxyl. And that lack of euphoria possibly blocked by naltrexone therapy.

Yeah, in that context. But you can see here, can't you, that this compound that has now two levels removed from the original herbal compound that he started now needs quite significant medical intervention to enable detox. So there clearly is a social risk here if nothing else.
So another aspect we wanted to look at was another report actually that came out I believe the following week also on the morbidity and mortality weekly report and that is looking at a phenomenon that I wasn't aware was a thing and that is the availability and the co-use of kava compounds alongside mitragynine to the point where they seem to be being supplied sometimes in combination products.

Now, kava is an absolutely fascinating compound. It is a root that grows in places like Fiji and it's consumed ritualistically. You dry it out, you grind it up, you mix it with water, and people take it orally. It reduces your anxiety.

It leads to mild euphoria. But it's been a compound that's actually been on the sort of wellness scene on the periphery for quite a few years. Certainly going back to the early 2000s in the UK. I was aware of at least one health food shop that would sell kava infused honey really as a wellness product.

But in the early 2000s there was warnings put out about hepatotoxicity and there was a bit of a crackdown actually certainly in the UK on the sale of kava compounds as food stuffs. It seemed to sort of humming in the background in the US and there was a rise in kava bars and now the kava seems to be being packaged alongside these mitragynine compounds and it's certainly occurring in similar sorts of markets. Again, when I was looking online this morning, I was able to find sites selling me mitragynine, 7-hydroxymitragynine, and also drinks containing kava compounds.

So, we're going to look now at this report, which looks at the co-occurrence of these compounds. So, this report again looks at national poison data system data from the 1st of January 2000 to the 31st of December 2025. It looked at exposures to kava and covered either single substance or in combination with other substances. Over this period, there were 3,111 kava-related exposures that were reported.

And between 2000 and 2001, there were 298 and 331 reports, which then began to decline, reaching a low of 42 in 2010, and then there was an increase back to 203 by 2025. Females accounted for the majority of exposures reported between 2000-2001, but in 2025, the majority of exposure reports involve males. 25% of exposures between 2000-2001 involved those under the age of 12, but this declined to 7% in 2025. Adults aged 20 and over accounted for the largest percentage of exposure reports ranging from 41% to 81%.

An average of 20% of exposed individuals were hospitalized each year and this didn't really change but the percentage of exposures associated with the serious medical outcome increased from 12% in 2000 to 39% in 2024 and eight deaths were reported across the study period. 43% of kava-related exposures involve multiple substances with ethanol and benzodiazepines being the most common co-exposures, but in 2017 kratom emerged as a common coexposure and surpassed both ethanol and benzodiazepines in 2019. In 2025 ethanol and benzodiazepines accounted for 3% of multiple substance exposures while kratom accounted for 30%.

The most common clinical effects among single substance exposures were gastrointestinal effects including vomiting and nausea, neurological effects including drowsiness, dizziness, lethargy and agitation and cardiovascular effects including tachycardia. Multiple substance exposures involving kratom and kava had similar symptoms. However, seizures and tremors were also noted along with hypertension. Liver injury was a less commonly reported effect, but moderate increase in both AST or ALT was reported in 1.7% of single substance exposures and 6.3% of multiple substance exposures involving kava and I think we might have to do a full deep dive episode on kava.

I think so because the relationship between kava and liver disease is complex. kava comes in a lot of different varieties and you get noble varieties and non-noble varieties and some seem to cause liver disease and some don't. Well, we'll do a proper whole episode looking at kava because it is fascinating. But there does seem to be this increase, doesn't there? There is this increase in exposures whereby kratom and kava are seen together.

And this possibly reflects the marketing. As I say, they're being sold certainly off the same websites. I've not been into a US smoke shop. My understanding is they're also being sold in US smoke shops alongside one another.

So there probably is this co-availability to a similar demographic. But I think also they both inhabit a similar niche, don't they? They are both natural compounds and they are sold a little bit as a wellness compound or a tonic rather than being a drug that you buy in a small white plastic bag from a guy on the corner of the street. They conjure very different images, don't they?

And it does seem that at least together possibly the risks do increase compared to single substances. Is that supported by the data? Yeah, I think so. And we need to think a little bit about pharmacology here, don't we? kava isn't the same as a benzodiazepine, but it acts in a similar way to benzodiazepines.

It acts via the GABA receptor pathway. Mitragynine, as we've already said, is an opioid. It has opioid properties. It's likely a partial agonist, at least traditional mitragynine, and it certainly doesn't behave in the same way as fentanyl for example, but ultimately it is an opioid.

We know mixing benzo and opioids is generally a bad idea and that seems to be what's happening here. So now we've got a couple of cases of people who were taking both kratom and kava and experienced withdrawal. The liquid blends of kratom and kava mixes are being sold and these are labeled as Feel Free classic tonic Blue Raz and K-Fusion and these contain 520 milligrams of kavalactones and dried leaf kratom with effects being experienced in 10 to 15 minutes and lasting approximately 3 to four hours. So the first case involves a male in his mid-60s with major depressive disorder, alcohol use disorder, and daily use of 30 milligrams of diazepam for general anxiety disorder who started to consume a bottle of feel-free classic tonic daily as he thought this was a healthy alternative to alcohol.

His use began to escalate and he eventually consumed 15 to 18 bottles daily. 3 days prior to his admission, the patient was given an ultimatum from his family and stopped the diazepam and the Feel Free classic tonic. The night of the admission, the patient took 80 milligrams of diazepam and drank a bottle of the tonic. In the emergency department, he was noted to be sleepy but orientated.

On day two, he was reported to be drowsy. And by day three, he had dispersed seizure-like activity. In the afternoon, he had another seizure-like episode and was found foaming at the mouth with locking of the joints and after it was over became more confused. lorazepam and diazepam were given and over the next two days, the patient had persistent borderline tachycardia and hyperactive delirium with hallucinations requiring physical and chemical restraints. On day six, the addiction medicine team were contacted and noted hyperreflexia, which is exaggerated reflexes often associated with CNS depressant withdrawal.

An oral diazepam was increased to 20 milligrams every 6 hours with suspected sedative withdrawal. The patient did begin to improve and by day nine he was back to his baseline. So before we dive into the second case, this was not only kava and kratom withdrawal. This was also diazepam withdrawal and 30 milligrams a day is not a small dose of diazepam.

Okay, he clearly had a lot going on, not just the one compound. The second case involves a male in his 50s with alcohol use disorder, major depressive disorder, and generalized anxiety disorder who transitioned from illicit opioid use to kratom use 10 years prior to admission. 3 years prior to his admission, he transitioned to drinking two bottles of Feel Free classic tonic daily and increased his use to 12 bottles daily. He did try quitting but was unable to and reported worsening auditory hallucinations.

He was continuing to consume 12 bottles along with a fifth of a bottle of whiskey and his last consumption of Feel Free classic tonic was on the day prior to his admission. On the day of his admission he endorsed suicidal ideation, paranoia and visual hallucinations of demons. He was tachycardic, hypertensive and exhibited minor leg tremors. He had a blood alcohol of 0.31 grams per deciliter and a urine drug screen was positive for benzodiazepines which he denied using.

He was then given 10 milligrams of oral diazepam every six hours and he was then started on buprenorphine/naloxone and 200 milligrams of quetiapine at bedtime. Quetiapine was increased on day two due to persistent paranoia and hallucinations and the diazepam was also increased to keep the clinical institute withdrawal assessment score below 8. On day four, all hallucinations had resolved and suicidal ideation improved and diazepam was then tapered. The patient was discharged on day seven with 16 milligrams of buprenorphine and 4 milligrams of naloxone and 300 milligrams of quetiapine at bedtime.

And it seemed that kava withdrawal symptoms were similar to those of sedative withdrawal and agitation was a common denominator in both cases. And it's perhaps not surprising, is it? If kava works by activating the GABA pathway, as I say, it does work differently from benzo. It doesn't bind at the same subunit or anything like that, but it does seem to activate that same pathway in the same way that alcohol does and GHB and a lot of compounds. it would make sense that withdrawal would probably have that similar rebound effect including agitation, seizures and so on.

As I say, kava is a fascinating compound and I do think we should do a whole episode really properly looking at it. But I am really interested in this rise in kava or at least this increase in its notability within people who are presenting to either medical facilities or calling the poison control and so on. I don't know whether this is just an increase in marketing or and this is now hypothesis time but perhaps actually there might be information out there about this. I haven't looked into this.

Are we starting to see a rise in semi-synthetic kavalactones? Ooh. Yeah. Traditional kava is this root.

It's a powder. You put it in a straining bag and you mix it with water and you drink the water. We're not looking at that. We're seeing extracts.

We're seeing tinctures that contain concentrated kavalactones. The exposure people are experiencing is not the in inverted commas natural form. Actually, you're seeing this enhanced form. I mean, we've been doing this for drugs for years.

Cocaine isn't a white powder. Traditionally, cocaine is a relatively low abundance alkaloid found in coca leaf. What we think of as cocaine is that's then been extracted and concentrated up into its more pure form. Similarly with compounds like opium, we've converted that to morphine and heroin.

I wonder if we're going to see the same with kava. I wouldn't be surprised if we start seeing semi-synthetic variants of kava appearing on the market. Possibly, as kava seems to be quite commonly mixed with kratom, you're going to get semi-synthetic mitragynine-like compounds and semi-synthetic kava compounds being merged together which I think would just be a recipe for disaster. It's certainly possible, isn't it?

Yeah, it certainly doesn't sound like a great idea. Well, I guess time will tell. I'm slightly shocked at the graph. The graph for the kava exposure was nowhere near as steep as the mitragynine increase over the last 12 months, but there was a clear increase in kava over the last few years.

There was a clear decrease when the original warnings about hepatotoxicity came out. And then over the last 3 or 4 years, there's been a steady increase. It'll be interested to see what that graph looks like in another 12 months and whether that has increased again. So, we'll see you again next April to have another look to see what's going on with the kava and mitragynine market.

It is a really interesting market, isn't it? It does seem to be really limited to the US. There are plenty of websites that claim they will sell kratom and kava outside of the US, but this high street smoke shop, wellness shop, tonic shop, whatever you're going to call these things, it's not something that we tend to see certainly in the UK because we've got the novel psychoactive substances act. But also the coexistence of these compounds does seem to be really quite a niche finding within the US.

I want to dive a little bit into that amphetamine immunoassay positive. Did they ever explain that? Apparently, kava is known to cause false positives on amphetamine immunoassays, which I didn't know. That's interesting.

Okay, so that's one to watch as well. If you get a surprising false positive amphetamine immunoassay to be fair, lots of things cause surprise false positive. Yeah. Amphetamine immunoassays.

But that is a good one to have in the back of the knowledge to know that might be a thing. And I know that the latest advice from the CFSRE on what compounds people should be looking for particularly in the US obviously it's aimed at the US includes some kavalactone compounds. So there clearly is increasing awareness of kavalactone being a contribution to toxicity. I think it's interesting.

I think we will see where this market goes and we will see where we are in a year's time. I wouldn't be surprised if there are moves to try and control some of these semi-synthetic derivatives. I know they've talked about it already, haven't they? Yeah.

And I’m not quite sure where the US law has got to over that, but I wouldn’t be surprised if there are some moves towards control of these compounds, but currently it appears to be a free-for-all. Very true. Well, I hope that’s been an insightful look at the mitragynine market. As I say, this is not something we’re mega familiar with.

We seem very occasionally in the UK. I would love to hear from our listeners in the US about what their experiences of this are. So, please do get in touch. We really do appreciate all your feedback.

And if you do want us to do a deep dive into kava, please let us know. Comment down below, send us an email. We’d really love to hear from you. Hope you all have an amazing week and we’ll see you next time.

Bye.