Episode 45: Diarylethylamines - The Rise, Risks, and Disappearance of Ketamine Substitutes

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Transcript

I'm Rebecca. I'm Rob. This week we're going to be talking about a family of drugs that swept the UK, left at least 37 people dead and then disappeared again. This is the story of some of Ketamine's strange cousins.

So Rebecca, strange relatives, do you have any of those? I think I probably have a few. Yeah, you going to name any? No.

No. Not that any of them listen, but just in case. I've definitely got some strange relatives and some of them do listen, but I'm not going to say who they are and now they're all going to think it's them. Yeah.

So as I say, this week we're going to be looking at an obscure class of drugs called diarylethylamines, or phenidines, which is much easier to pronounce. This is based on a paper that's just been published, which was a systematic review and a really solid review of all published cases involving these drugs. 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 LinkedIn page, which we're fairly active on 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 about our episodes, you can email us at thetoxlab@gmail.com. So Rebecca, why don't we look at this paper? It's relatively hot off the press, isn't it?

It was published a few weeks ago and it's a review of data, looking at global deaths related to these compounds, but in the window of 2014 to 2019. So it's pretty much a history lesson, isn't it? We're looking back at some data that was collected over a long period of time, some time ago. So I want to have a look a bit at the history of phenidine drugs.

Difenidine was first synthesized in 1924 in Germany by researchers looking for novel anesthetics in the 1960s, 70s, 80s. There was a renewed interest in NMDA antagonists. And in 1989, methox phenidine was actually patented as an analgesic candidate, but it never made it to market. And for both of these, the chemical literature was published.

So it wasn't too difficult further down the line for chemists to rediscover it and know how to synthesize it. So back in January of 2022, the advisory council on the misuse of drugs were commissioned by the UK government to advise on appropriate classification of phenidines under the Misuse of Drugs Act. So this paper is part of the research that went into that report. So they initially conducted a literature search and looked at papers with cases published between 2015 and 2018.

So in total, they looked at five different diarrhile thalamines, including difenidine, effenidine, methoxphenidine, fluorolintane, and isofenidine. And it is important to note those go by a couple of different names as well. So it can get a little bit confusing. So from this literature search, they had 18 cases with enough detail, which included five deaths in England, four in Japan, and the US, two in Wales, one in France, one in Germany, and one in Hungary.

From this data set, 15 out of the 18 individuals were male with a mean age of 35, 11 were found dead at home. And smoking or inhalation of these substances was likely the root of administration. Some

findings on autopsy from these cases showed enlarged hearts and hypertensive heart disease. In two cases, enlarged heart and mild arthroma in two, there are multiple injuries in some of these, and one had signs of drowning.

And the most common cause of death from this data set was poisoning involving quite often other substances. So I want to take us back to where these cases first started, 2014. Happy by Farrell Williams had actually come out the year before, but was at this point on every radio, everywhere. Couldn't go anywhere without hearing that song.

Greg's sausage rolls were entering meme status. On the drug scene, ketamine had been reclassified the year before from a class C drug to a class B drug. And there were head shops on every high street. Selling legal highs because, of course, this was pre the novel psychoactive substances act.

And in light of that ketamine scheduling, ketamine analogs had started to appear. And this is where the phenodenes have started to emerge. So what are they? Well, they're related to ketamine.

They behave in a similar way to ketamine. Chemically, they're slightly different. Ketamines built around a six-sided cyclohexyl ring, which acts as the backbone. Whereas the phenodenes have got two benzene rings bolted onto an ethyl chain.

So they're chemically distinct, but they're similar in structure really. And they act in the same way. They act as what we call NMDA receptor antagonists. There are, however, differences in what users report.

In particular, phenodenes have a reputation for lasting a lot longer than ketamine. So whilst ketamine might be active for an hour or two, people describe some of these phenodenes as lasting eight, 12, sometimes even 24 hours. They also describe the feeling as very different from ketamine. They describe it as muddy, dark, but also people describe repeat dosing and compulsive redosing.

There's been some clinical effects described as well. So paranoia is reported. Amnesia is quite common. People can't form memories whilst taking these drugs.

But also people have presented to hospital following the use of these drugs with tachycardia, hypertension and seizures. So Rebecca, why don't we drill a bit into some of the data in this paper and have a look at some of the cases that were reported. So between 2014 and 2019, they found evidence of 48 deaths worldwide as a result of these substances, 37 of which were in the UK. From the UK dataset, diphenidine was found in five cases.

Methoxphenidine was found in 31 and there was one case that involved both of these drugs. And they managed to find enough information on 35 of these cases. The majority of which were male with a mean age of 37, 72% had a history of drug use and 71% were prescribed other drugs including gabapentinoids, antidepressants, benzodiazepines, opioids, beta blockers, antipsychotics and antiepileptics. In 33 out of 35 of these cases, the cause of death was acute toxicity or intoxication.

And it was quite evenly split as to whether people were just using the diphenidine or the methoxphenidine or MXP. So 14 cases involved just those drugs and 15 involved the diphenidine or the MXP with other drugs. In six cases, MXP was implicated alone and the levels were quantitative and was found to be present at a mean concentration of 7.92 milligrams per liter but there was a range of between one and 24 milligrams per liter. In two other cases, MXP was quantitative where other drugs were also implicated and the mean was lower at 2.84 milligrams per liter.

Diphenidine was only quantitated in two cases. So in one case it was found a concentration of 1.67 milligrams per liter and in the other it was found at a concentration of 2.4 milligrams per liter but that case didn't specify what tissue was used for quantitation. So overwhelmingly male population and a bit

of a 50-50 split between whether these were polydrug cases or whether these were single drug intoxications. The fact that there were any single drug intoxications at all in this dataset is fairly unusual, isn't it?

Ketamine does kill people on its own but actually not often. Often that's mixed with alcohol and other drugs. To see so many cases with the ketamine analog being reported on its own could suggest a higher degree of toxicity compared to ketamine. Should we have a look at some of the cases that were reported?

So this first case involves a 34-year-old male who was founded at home. At the scene there was evidence of drug paraphernalia including white powder in clear bags that was later identified to be methoxifenidine. At autopsy he was found to have an enlarged heart and hypertensive heart disease with no other contributory findings. And based on this preexisting heart disease and the potential cardiac effects of two methoxifenidine this drug was considered to have likely contributed to the death.

They did quantitate the drug in this case and it was found to be present at a concentration of 24 milligrams per liter. And the only other drugs of note were his prescribed meds which included mirtazapine, lamotrigine and citalopram all present at therapeutic concentrations. So in the absence of any other medical cause it was thought that the methoxifenidine was likely to be the culprit. Yeah.

A couple of the cases in the series involved individuals either jumping or falling from bridges. There was one involving an individual who drowned in the bath after using methoxifenidine. It's quite a range, wasn't there? Ranging from direct toxicity, possibly cardiac toxicity to deaths associated with disassociation, people falling, people drowning in bathtubs.

It does seem that the prolonged effects may carry with them additional risk. Interestingly, I had a quick look at the ONS data for this period and I estimated there was about 180 ketamine deaths in this same period or at least deaths where ketamine was mentioned. So obviously this is a relatively small number compared to the ketamines. But I think a key piece of this puzzle here is we don't know how many people were using these phenidine compounds in this time period.

Well, what happened after 2019? Well, in 2016, the UK enacted the Novel Psychoactive Substances Act, head shops closed overnight. In 2021, the UN scheduled diphenidine. So as quick as they had emerged, they seem to disappear again.

So why do phenidines have different subjective effects? What's going on? I'm not sure we necessarily know the answer to this. Although both phenidines and ketamine are NMDA antagonists, we know ketamine has a load of other downstream effects, don't we?

It's possible that there are some off-target effects affecting the phenidines. This really is an interesting data set, isn't it? It shows us the cycle that MPS, Novel Psychoactive Substances go through from filling a gap in a market to proliferating, to disappearing from obscurity. There's some really interesting nuggets in this data set, isn't there?

Firstly, that we see a relatively high number of single drug intoxications, which is unusual for disassociative drugs. The other interesting point here is that so many of these cases seem to be focused in the UK. Why is that? I mean, it could be one of a couple of things, either we're just picking them up and talking about them, and there's this data that's widely available, or I guess with a lot of drugs that are more prevalent in, for example, the States, this just could be one that's very popular in the UK and nowhere else.

When we were listening to Farrah Williams and eating Greg's sausage rolls, we enjoyed disassociative drugs in the UK. Yeah, because why not? It's certainly a good point, isn't it? The social context at the time, I think was possibly important, the fact that we had controlled ketamine, but we did have these high street shops.

It just filled a natural gap in the UK, but also these are really obscure drugs, probably not that many labs. At the time, we're going to be testing for them. Not everywhere had high-res accurate mass screening that we've got now. So a lot of labs globally would have had a much narrower screening scope.

So it's certainly possible that there were a lot more cases that weren't picked out for sure. It'd be interesting to know whether these drugs have truly gone away or whether it's just a flaw that they're not killing people so we're not detecting them in post-mortem toxicology, but they could still be being used recreationally and we just have no idea of how prevalent they are. It's certainly possible. I think the fact that there were so many single drug intoxications in this dataset makes me think probably we would have seen them, but yeah, it's a fair point, it's a fair point.

Another thought I have had is with the cardiac effects of these drugs, that's unusual as well, isn't it, for NMDA antagonists. We certainly don't see hypertension to the degree that has been reported with these. Does it mean there's some other pharmacology going on? I'm not sure how well these compounds have actually been tested in receptor assays.

Is there some other receptor that they are hitting? That is a fair point, quite possibly, as they do seem to be having this other effect that isn't generally associated with NMDA antagonism. So where does this leave us now in 2025? Farrell Williams is still on the radio.

That song never really went away, unlike the Phenadines. But are we at the cusp of history repeating itself? We talked a few weeks ago about ketamine, didn't we, and how there is an increase in ketamine use, particularly amongst young people. There are talks of further control on ketamine, considering upgrading it to a class A drug from a class B.

Will we see a new wave of phenadines, either these compounds or chemically altered phenadines or some other ketamine analogs? I think we are at real risk of something filling that gap if ketamine does become more controlled. We see it with a lot of other drugs, that things will always fill that gap. I have to watch the space and see what it is.

And if it's a phenidine, possibly, that's going to come with increased risk. So in summary, this paper really was a nice little historic look at the life cycle of an NPS and a real classic case study of how a drug can be rediscovered from an old pharmacy patent to filling a niche in a drug market, to causing measurable harm, to disappearing into obscurity again. And this is a cycle we see repeating over and over. I hope you've enjoyed listening this week.

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