Episode 62: Methaqualone (Quaaludes) - From 1970s Sedative to Modern Analogues

Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're gonna be taking a look at qualiudes and qualiude analogs. Before we dive too hard into today's episode, I thought I'd take a slightly lighter look at qualiudes, in particular, what I think most people's experience of qualiudes is.

And that's not experience of the drugs themselves, but actually that one particular scene from the Wolf of Wall Street. You know the one I'm talking about, right? Yeah. For context, Leonardo DiCaprio's character had taken some qualiudes that were long out of date, and suddenly they hit him right at the wrong moment.

And there's this incredibly painful scene of him crawling down some stairs towards a Lamborghini. And I'm just sat there thinking, I really hope he doesn't get in that car because the last thing we want is for him to drive. And this was very much a dramatized version of what qualiudes can do. But this week, we're gonna be looking at the realities, the history, and also the emergence of some newer analog versions of this classic iconic drug that disappeared many, many years ago.

And this episode is very kindly sponsored by Cayman Chemical. And Cayman Chemical provide a wide variety of resources for scientists, including biochemicals, assay kits. One particular product line they sell is reference materials. And as a toxicologist, I can honestly say we'd be lost without their reference materials.

Their material catalog is exceedingly wide and they're really good at responding to new compounds as and when we in the lab need them. So we'll put a link in the description below. Do go and check them out. So when we're talking about qualiudes, what are we talking about?

Well, qualiude is actually the brand name. It's actually derived from two words, an amalgamation of quiet interlude. Oh, okay, didn't know that. And they were essentially sedative drugs sold in the 1960s, originally marketed as a safer alternative to barbiturate drugs, which were relatively commonly being used as sedatives at the time.

The chemical name is methacrolone and the effects are broadly similar to barbiturates, alcohol, benzodiazepines. They potentiate the inhibitory neurotransmitter GABA. So they act as an allosteric modulator. And when they were used pharmaceutically, they had quite a narrow therapeutic window.

And the history is interesting because it was originally synthesized in the 50s as a malarial candidate. And it didn't work very well as an anti-malarial, but as often the case with a lot of drugs, it did find use doing something else. And it was sold as a sleeping tablet, anxiety treatment. Marketed as, A, it's not a barbiturate.

And there was a lot of issues with barbiturates at this point in time. And also marketed as a safer and less addictive version. Spoiler alert, turns out might not have been any less addictive. And it saw a big cultural use as well.

In the 70s, early 80s, it saw a lot of recreational use as a sedative. It developed a lot of nicknames, ludes, disco biscuits. And users really sought it for the euphoria, the muscle relaxation. It was big on the disco scene, particularly I think at the end of the evening where people were wanting to come down from their partying.

But it also had a very dark side. There was quite an overdose risk, particularly if you mixed it with alcohol. It was also quite widely used in drug-facilitated crime as well. And so throughout the 70s and early 80s, it became more and more controlled.

A lot of countries banned it completely outright. And it's now globally, there's no legitimate manufacturer. So why are they still famous? Well, I think it's probably looked at through a bit of a historic lens.

There's a certain nostalgia. Films like The Wolf of Wall Street probably glamorize it a little bit. And I think most people really know the myth rather than what was the truth at the time. But this week, we're gonna be looking at some papers that look at methaquilone analogs because these seem to be or have been emerging over the last few years as potential novel drugs that may be trying to capitalize a bit on some of that nostalgia, but also possibly filling a little bit of a void now that some of the benzodiazepines are becoming more restricted.

So we're gonna be looking at some of the limited data out there. There's not a lot of data on methaquilone analogs, user experiences, and also their appearance in toxicology casework. So Rebecca, why don't you dive in? So the paper we're looking at today is a review of the experiences of users of methaquilone and methaquilone derivatives.

And this data draws on information from online drug forums such as Reddit, BlueLight, and DrugsForum. Encyclopedic drug sites such as Aerowid and Psychonaut Wiki, and also drug checking services including Widenos and DrugsData. They went through these sites and looked at different threads and selected those based on popularity and engagement, and they were focusing on areas involving routes of administration of these drugs, doses and duration of effect, desired effects versus adverse effects, and sort of real world experiences.

So first taking a look at the chatter around methaquilone itself, it's typically used orally and taken in tablet or capsule form with 150 to 300 milligrams being the typical dose, but this often seemed to escalate with chronic use. Effects at low doses included sedation, relaxations of anti-anxiety effects with high doses leading to euphoria, dizziness, nausea, increased libido, muscle relaxation, and amnesia. But severe intoxication needed to lots of negative side effects such as loss of motor control, unconsciousness, and respiratory depression. So this is the actual methaquilone itself.

This isn't an analog, is it? So as I said earlier, it is globally controlled, but it does still emerge occasionally through illicit production and sale. It's also possible for people to find old tablets in the back of cupboards, and that's definitely been reported on Reddit a few times as well, doesn't it? Other routes of administration included smoking.

This was reported to often be mixed with cannabis and was quite notable in South Africa. Routes such as intranasal, sublingual, and injection were less commonly talked about and often were reported coming with a higher risk of negative side effects. There's also a lot of illicit synthesis discussions happening online, but the synthesis pathways to synthesizing methaquilone often involve otolidine, which is a highly carcinogenic precursor, and it's thought that this might have increased the intentional and unintentional use of these analogs to try and bypass that quite toxic synthesis pathway.

Actually, interesting you mentioned South Africa there, because in general, qualities are not commonly found substances, even though they do emerge occasionally, as we're going to talk about as analogs

and small clusters of cases. The outlier is South Africa, where South Africa seems to have quite a lot of illicit synthesis of methaquilone. So the first analog we're going to talk about today is called SL164, which is a catchy name. It's actual name is Diclocholone, which is a dichlorinated analog that first appeared online in 2019.

It was initially praised for its GHB and carasopridol-like effects when taken orally, but it had a major red flag of causing seizures and convulsions, even at quite low doses. Effects often peaked around 45 minutes after or an ingestion and lasted several hours. Smoking and snorting this often resulted in no effect. And this drug was associated with quite severe motor impairment, loss of consciousness, and paralysis.

It was often being used with alcohol, and this often worsened these effects. Seizures of this drug in Europe found that it contained four chloro-o-tolidine, which is another carcinogenic compound and contributes to quite severe bladder toxicity. And they did find two cases of SL164 poisoning that had been reported in the literature. So case one involves a 22-year-old male who consumed 300 milligrams alongside opium poppy tea and was admitted to a poisoning treatment center in Germany in 2019 with myoclonic convulsions, tachycardia, dilated pupils, and altered mental status.

But his symptoms did resolve after 72 hours. The second case involves a 21-year-old male in the US who presented to the emergency department after consuming 600 milligrams of methacrylone and 500 milligrams of cocaine, but lab testing revealed that he'd actually taken SL164. He developed drowsiness, myoclonic jerking, methemoglobinemia, and this was thought to have been caused by the four chloro-o-tolidine precursor, which was undergoing metabolic activation to form a substance that induced hemoglobin formation. That is possibly a really, really useful nugget of information.

If you've got a patient who's taken an unknown substance and has methemoglobinemia, I'm going to be thinking about possible methacrylone analogs now. The fact that this compound can cause seizures is quite interesting. Methacrylone has been implicated in seizures in overdose. In general, it's got an anti-convulsant effect at therapeutic doses, but it does seem to have this higher-dose, pro-seizure effect.

I'm not sure I quite understand the pharmacology. Yeah, and it seems to be a recurring theme with a lot of these analogs that they do cause seizures at lower doses, so probably due to potency. So the next analog we're going to chat about is nitromethacrylone. This was once marketed in Europe and was approximately 10 times more potent than methacrylone but was withdrawn due to mutagenicity, side effects.

And it reappeared online around 2018 despite all these warnings that are going around. People still seem to want to get their hands on it and use it. Users reported euphoria, relaxation, and anti-anxiety effects. Tremors, dizziness, loss of consciousness were also reported and all doses were around 25 milligrams with intranasal doses being between 30 to 40 milligrams with a rapid onset of effect.

Babroquilone, or MBQ, is another analog. It's the brominated analog that was first developed in the 60s but never approved medically. It was reported as an MPS in the UK in 2013 and forum interest peaked between 2013 and 2019. It's reported that oral and intranasal use largely elicited no effect with smoking and vaping producing a rapid intense effect lasting approximately one hour and physical effects seem to last longer than the psychological ones.

High-dose toxicity included severe lack of coordination, impaired vision, nystagmus, numbness, severe limb and whole body twitching, and short-term memory impairment. Repeat dosing was often reported on these forums and was of concern along with the use of MBQ with other depressants such as alcohol to enhance this effect. Two real-world cases were reported in the literature and these come

out of the US in 2018 where MBQ was detected in biological material. In one case, the individual had died in a fire and MBQ was detected at a concentration of 10,228 nanograms per millilitre alongside lorazepam, oxycodone and difenhydramine.

In the second case, a man had jumped in front of a train and had an MBQ at a concentration of 115 nanograms per millilitre in addition to methamphetamine and amphetamine. So both had this compound present. Hard to determine from the circumstances whether it was having a toxic effect or not because all sorts of other things going on in the case. Finazone is a novel isomer and it's been mentioned online since around 2013 with an increase in the number of reports between 2020 and 2023.

It was detected in Germany in 2021 and made it to the EMCDDA early warning system. Again, all routes were largely reported as being ineffective with smoking and inhalation being preferred. And there were fewer physical side effects reported compared to other analogues though the data on this is really, really sparse. Methylmethaqualone, or MMQ, is the most frequently abused analogue.

It was first reported in a seizure in 1993 and has been heavily discussed online. It has similar effects to methaqualone when taken orally but is more potent when smoked. But what's important to note with this one is the recreational dose is reportedly very close to the seizure threshold. There appears to be one single report in the literature that was mentioned in this review and that's of a 24 year old man in 2012 in Switzerland who was admitted to the emergency department after taking two 500 milligram MMQ tablets.

He developed CNS depression, psychomotor agitation, muscle overactivity and tachycardia. And the patient was readmitted a few days later after taking the exact same dose of MMQ again. The final one mentioned in this review is etaqualone, or ETQ, and it's an ethyl derivative of methaqualone. It's a former insomnia drug in Europe and is still used medically in China and was reported as an NPS in Denmark in 2009.

Users reported it to be a weaker and shorter acting version of methaqualone and is often compared to gabapentin, baclofen and alprazolam. It has been spotted as a replacement for methaqualone in the illicit Chinese drug Yu-Yu. You've probably completely butchered that. And this typically contains methaqualone and ephedrine but its components are inconsistent and chlorpromazine, caffeine and diazepam have also been detected in this mix.

So quite a number of different compounds that have all been detected all describing something really similar, aren't they? Typically more potent versions of methaqualone often doing similar things to what methaqualone would do. Although there seems to be an increased risk of seizures with a lot of them, which is clearly a problem. Yeah, I found it quite interesting looking at all these analogues that in user reports, some of them seem to elicit an effect when used orally, but for some of them that didn't cause any effect and smoking was the preferred route of administration.

And it's interesting how the different modifications on that compound mean that one route of administration versus another produces the desired effect. Yeah, that's definitely interesting. So I guess the question is, we know these things exist. There's very little data out there, which suggests either they're relatively rare compounds or the other possible alternative is just nobody's testing for them.

But my suspicion is actually the former that there's not a lot of use of methaqualone analogues. The big question is, are we going to see them emerge? I'm just thinking in terms of context, looking at the history, the disco emergence came in the 70s following the amphetamine scene in the 60s. People went from partying hard to wanting to come down and calm down in the evenings.

We've seen cocaine purities go up and up and up. We've seen novel benzos actually coming under a bit more control, bromazolam being restricted, not necessarily anything filling that gap. Are methaqualone analogues next? I mean, I guess it's just a case of watching the space and seeing if they do appear, something's gonna fill that gap in the market eventually.

What I did find interesting was some of these compounds are not new, some of these dates were mid 2000s, I think you said. What was the earliest? Yeah, some of them were reported to be seen from like 2009 onwards, but a couple of them were developed back in the 60s, either never made it to market or made it to market for a very short period of time before they were pulled. So not new compounds, but potentially could suddenly become an emerging thing.

And I feel like that's been a recurring theme that we keep seeing this emergence of drugs that were developed back in the 60s that have been long put on like the dusty top shelf and then someone's come along and has rediscovered them and decided to produce them. So who knows what else is in that library of old drugs that were never really seen. That is true. Yeah, that is always the risk.

And we didn't actually touch on this when we talked about the history, but methaqualone, the licence, was owned by a company called Lemmon Pharmaceuticals. And another name for methaqualone was Lemmons. These tablets were considered iconic. Lemon 714, they were stamped on the tablets.

If you go on the WEDINOS website and look at some of the submissions that contain methaqualone analogues, a lot of these are white tablets stamped with Lemon 714. None of them contain methaqualone. They all contain analogues. They are all modern counterfeits, but they're leaning into that old marketing of the 70s.

And do you think The Wolf of Wall Street has kind of glamorized these things a bit and perhaps produced this nostalgia? I think so. Another point that was brought up in that review paper was that there's lots of chatter kind of around the pop culture association of methaqualone and how people look back on that era and the use of it really fondly and in a very positive light. And it's probably a lot of looking through things with rose-tinted glasses.

Yeah, I think that's fair. And there's two sides, isn't there? There's that side, which is driving the market. But you've also got producers leaning into that nostalgia and using it as a marketing technique effectively.

And we touched on it a little bit, didn't we? But I wanna dive a little bit into South Africa because South Africa is really the only place where methaqualone is commonly a thing or at least more commonly a thing than everywhere else. Typically called Mandrax. A lot of local manufacturing occurring there and a lot of its use amongst particularly sort of poorer populations.

It really is a bit of a global outlier actually. So where does this leave us as toxicologists then? They're clearly a thing. They're not a common thing.

Where does that leave us? It's tricky. I feel like it's one of those classes of drugs that you just need to keep in the back of your mind, especially in like a clinical setting if you've got someone presenting with seizures and you know they've been taking something that they've bought. It's just something to be aware of and to go hunting for.

But the problem is with all of these different analogs, you never really know what you're looking for. There's always the chance it's gonna be something new that's never been reported before. So it does just make the whole thing so much harder. They are relatively non-potent, aren't they?

We're looking at relatively high doses compared to a lot of drugs, milligram doses, many milligrams. And some of those case reports, we're reporting what, 10 milligrams a litre in blood? If you're using

high res screening, you might actually be able to see a big rogue peak when you're total ion chromatogram. I think all in all, they're really interesting class of compound.

They've got some really interesting pharmacology. I'm not sure I understand why they can both suppress seizures but then at higher dose cause seizures. And I don't know if that's really that well understood. I think it'll be interesting to see whether they do emerge or whether they'll just remain as they seem to have done over these last 10, 15 years as small anomalies that will just crop up from time to time either in acute hospital admission here or post-mortem case there rather than taking a big mainstream place rather just continuing to appear in isolated cases.

If that does happen, it makes it even harder to kind of stay on top of them really, doesn't it? So I think in summary then, they are a thing. We need to think about them. They're probably not a huge thing yet but who knows what the future holds as always.

I wanna thank Caiman Chemical again for sponsoring this episode. We really do appreciate it. Do go and check them out. As I say, they have a wide range of products and resources that may be of benefit to a lab including a number of these methacrylonanalogs available as reference materials.

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