

Episode 27: Ketamine - The Good, The Bad and The Ugly

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TRANSCRIPT

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. So this week we thought we'd have a look at ketamine, a drug that was once really just associated with horses and ravers but has actually now seen a huge increase in its scope of use. Some people say ketamine is the best drug.

I think those people should get off their high horse. That was actually awful. But in all seriousness this week we're going to be looking at a few papers on ketamine. Before we jump into today's episode, just a quick reminder that all the papers for this episode will be linked in the description down below.

So if you want to do any further reading or check them out for yourselves you can find them down there. And a quick shout out for our socials: if you want to get in contact with us, give us feedback on any of our episodes or if you've got ideas for future episodes you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn. For those of you who don't use socials we also have an email address so you can email us at thetoxlab@gmail.com.

So Rebecca why don't we jump into the first paper? So the first paper we're looking at today is looking at IV ketamine treatment for depression in India. So some facts to start off with: 5.3% of people in India are affected by a depressive disorder and their suicide rate has increased from 9.9 per 100,000 people in 2017 to 12.4 per 100,000 people in 2022. So this paper is a retrospective chart review of in-patients with depressive disorder as per ICD-10 codes, which we've looked at previously, and these individuals received ketamine infusion therapy between March 2023 and September 2024.

So this included patients with depression and suicidal ideation, those who had treatment-resistant depression, which includes failure to respond to at least two different classes of antidepressants for more than six weeks at a maximum recommended dose. So to assess these patients before they had their ketamine infusions they used the clinician-rated Hamilton Depression Rating Scale-17, which has 17 items relating to symptoms of depression that an individual has experienced over the past week.

So you'll come out with a different score, so 0 to 7 is equal to no depression, 8 to 16 mild depression, 17 to 24 moderate depression and greater than or equal to 24 is severe. So these individuals were given 50 milligrams per millilitre of ketamine hydrochloride in a continuous IV infusion at a dose of 0.5 milligrams per kilo of body weight over 40 minutes. The number of sessions each individual received varied but they were given at least three as an induction and then in those who didn't respond to treatment, treatment was discontinued and they determined those who didn't respond to treatment as having a score that didn't change, essentially.

So from this chart review they found 28 patients that met the criteria. Mean age was 37 and 61 percent of them were males. Forty-three percent of them had recurrent depressive disorder, 29 percent had a single depressive episode, 25 percent had persistent depressive disorder and 4 percent of them were bipolar and half of them had at least one psychiatric comorbidity, so either generalized anxiety disorder, substance use disorder or panic disorder, and 86 percent of them had severe depression based on this score.

So ketamine's got a lot of medical uses. It's often used as an anesthetic in cases of trauma and things like that, but it's also seen use in treatment-resistant depression, hasn't it, so this isn't new groundbreaking stuff, this has been around a little while now. There are ketamine clinics around the UK using ketamine for treatment-resistant depression and so far I think a lot of the results have been fairly encouraging, haven't they? Yeah I think so.

So in this study a statistically significant decrease in score was seen post-treatment, so 15 out of the 28 patients achieved a greater than 50 percent reduction in their score and 11 of them achieved what they classed as remission, so they had a score of less than seven which is equal to no depression, and 80 percent of them had a substantial decrease in suicidal ideation as well.

So it seems like quite a promising effect and it seems like the ketamine infusion therapy has worked quite well in these people but it is important to remember that there were only 28 people in this review and they were also only looking at the effect 24 hours post-treatment so we don't really have any data on long-term effects and what that might mean days, weeks or months post-treatment. Yeah on the one hand this provides really good real-life data doesn't it? These are real patients that have undergone real treatment and shown a real improvement in their symptoms.

As you say it's a very short-term study, it was a retrospective study as well, so it wasn't perhaps an ideal clinical trial but this just adds to the wider body of evidence. There are a few studies now that have shown ketamine can be quite effective in achieving remission in depression which is, you know, as we're saying, depression that has not responded to other conventional treatment. I guess this short-term effect in this study does raise the question: is this just a sort of pause in symptoms rather than a cure, although I think some patients did go back and have multiple treatments.

Yeah as long as they were achieving some sort of reduction in their score they were continuing these infusions but I don't know for how long a period they were going back and forth, how long they could go before having an extra infusion and things like that. And as I said earlier there are now a few clinics certainly in the UK that are offering ketamine treatment. As far as I know it's not available on the NHS but it is medically supervised off-label because it's not approved for use in depression in the UK, but, you know, medically supervised use of ketamine for depression.

So overall then relatively positive outcomes to ketamine infusions in this context. Yeah. Is this one of the reasons why we're perhaps seeing an increase in use? Famously Elon Musk has admitted to using ketamine to treat depression.

Potentially. I do know that in the UK the Office of National Statistics have stated that ketamine use has doubled since 2016 and there's been a three-fold increase in use amongst individuals under 25. So very briefly I want to touch on the pharmacology of ketamine. We've talked a bit about NMDA antagonists previously.

So ketamine essentially blocks a type of glutamate receptor and that reduces the inhibitory tone on certain neurons. So you effectively turn off certain parts of the brain and turn other parts on. What's interesting about ketamine is that it seems to lead to an increase in brain-derived neurotrophic factor, which is a protein involved in neuron growth, and one of the hypotheses is that ketamine works as an antidepressant by effectively causing the brain to rewire itself a little bit.

Yeah, so unlike other antidepressants, which are more about ongoing symptom control, there is at least the theory that ketamine could potentially lead to longer-term changes within the brain, although I'm not sure we've got much data on that as yet. So why don't we move on to the next paper? The next paper we're going to look at today is about recreational ketamine use in individuals who have opioid use disorder. There is potential for ketamine to be used to treat opioid use disorder, and it has been shown to help with withdrawal symptoms and can also assist with cocaine-related cravings and withdrawal.

So this paper looked at data that had been collected from people participating in an opioid use disorder programme in the US. This included 93 substance use treatment programmes across 35 different states and covered people over 18 who were newly admitted to programmes, in order to avoid repeat data collection. From this survey they found 86 people who used ketamine and 215 who didn't, and in the group

of people who used ketamine they were more likely to be under the age of 45, more likely to be male and also more likely to live in suburban areas.

Sixty-seven percent of them used other drugs alongside ketamine, including cannabis, alcohol, cocaine, MDMA, psilocybin and prescribed opioids. And what I found interesting is that the mean number of drugs used alongside ketamine was 3.89, so there was quite a lot of polydrug use going on in this data set. So I guess the question was: were they using ketamine to self-treat their opioid use disorder, or were they using ketamine because they were also using everything else that they could get their hands on? Yeah, that is an interesting point.

Fifteen percent of them stated that they used it to ease opioid withdrawal symptoms and cravings, and 8% of them were using it to avoid opioid use altogether. So this is another emerging area, isn't it? Similar to the pharmacology associated with potentially treating depression, there is this idea that perhaps ketamine could help rewire the brain effectively and reduce some of the addictive behaviours and feelings that come with opioid use disorder. Yeah, it's interesting, isn't it?

Is this effectively self-treatment off-label use or is it effectively a coincidence under the polydrug use heading? I mean I guess it's probably a bit of both and it's quite a tricky picture to untangle because they could be using it partly for its recreational use and because it's a drug they can get their hands on but also because it does come with that added benefit of sort of treating withdrawal symptoms from other things.

Depending on the drug treatment programme they're in as well and what testing is being done, ketamine isn't always tested for so it might well be that there is a motivation among some to effectively try and dodge drug tests which are clearly going to be testing for opiates and things like that.

And out of the people who used ketamine in this study, approximately one third of them reported negative effects whilst on ketamine. I think about two thirds of those reported central nervous system problems, such as terrors and very intense episodes of dissociation, and some of them were even admitted to the emergency room or hospital as a consequence of this. So these were quite severe negative effects. Okay, so let's now move into our third paper. This next paper looks at ketamine use disorder.

So in individuals who use ketamine chronically, and at quite high doses, they can experience some significant negative effects associated with that. Ketamine use disorder includes a range of symptoms and can involve cognitive impairment, structural and functional brain changes, including a global reduction in grey matter volume, and individuals frequently report an increase in depressive symptoms. They can also get ketamine-induced cystitis, the severity of which correlates with increasing ketamine use.

GI issues are also commonly reported, and 25% of people experience symptoms such as abdominal pain, also known as K cramps, which can lead to a cycle of continued use because people then use ketamine as a way of treating the pain associated with these cramps.

But what's interesting is that not a lot of people are seeking help for these issues, so this paper notes that only about 50% of people are seeking care for bladder issues associated with ketamine use. They conducted a survey to try to see how many people who use ketamine chronically are experiencing ketamine use disorder and how people are going about seeking treatment for this. In total, 274 individuals with a history of problematic ketamine use or ketamine use disorder completed the survey, 179 of whom completed the entire thing, between November 2023 and April 2024.

So some general stats about the individuals who took the survey: 69% were current ketamine users, 60% of them were not seeking treatment at this point for their ketamine use or ketamine use disorder, 48% were male and 59% had been diagnosed with a mental health disorder. The average age of individuals taking part in the survey was 28. On average, individuals first used ketamine at about age 19, 98% of people were snorting their ketamine, and they were consuming an average of two grams a day, with as much as 20 grams being taken in a day.

Looking at usage between the treatment-seeking and non-treatment-seeking groups, the treatment-seeking group used a significantly larger amount of ketamine per day. And in effectively ketamine-naïve individuals, doses of 30 to 75 milligrams might be considered a dose, so we are talking either large doses or lots of

repeated dosing over the course of a day.

Seventy-three percent of individuals were using ketamine as their primary drug of choice and had been using it for between two and ten years. Initial motivations for use included wanting to dissociate, self-medicating for depression, and interest in the psychedelic effects, and people then continued using as a way to dissociate, to self-medicate and to relax.

So moving on to symptoms that people experienced with their ketamine use disorder, 13% of people who completed the survey reported no symptoms, 60% reported bladder problems, and just under that, 56%, reported K cramps, headaches and nasal issues. Other issues such as kidney problems, gallbladder issues, body aches, liver problems, heart palpitations, erectile dysfunction, brain fog and constipation were also seen. But a whopping 56% of them were not seeking treatment and, of those who did, only 36% felt satisfied with treatment for their physical symptoms.

So did this study look at ketamine withdrawal or anything like that when people did try to quit ketamine? They did. They asked people what sort of symptoms they were experiencing when they did this, so approximately 70% of people experienced cravings, low mood, anxiety, sleep disturbance, fatigue, abdominal pain and insomnia, but they also reported what I would consider more typical withdrawal symptoms, like sweating, shaking, palpitations, tremors and delusions.

So 41% of people who completed the survey had sought treatment for ketamine use disorder and what I found quite interesting was that people were going back multiple times to seek treatment.

So 38% of people sought treatment once, but 16% of people were seeking treatment more than five times. This included going to a specialist addiction treatment provider, but 36% of them were consulting their doctor, and the most common treatment options included outpatient therapy, support groups, inpatient rehab and holistic therapy. Most people found support groups, inpatient rehab and outpatient therapy most effective, but about 14% of respondents reported that no treatment was effective in treating their ketamine use disorder. It's really tricky, isn't it?

Addiction services probably aren't really set up to deal with ketamine as a substance. For opioid use disorder we've got established protocols using opioid substitution. For people with alcohol use disorder and benzodiazepine dependence again there's protocols we can switch people onto other benzos we can taper them. With ketamine there's not really anything that acts in the same sort of way.

There's no ketamine substitution therapy, and a lot of people who took part in the survey agreed with you. They think there is a need to educate healthcare professionals on ketamine use disorder because they felt that a lot of people didn't really understand what the problem was, and those who weren't seeking treatment actively emphasized the need for therapy and some sort of medication to aid quitting ketamine use. Those who weren't actively seeking treatment cited a lot of barriers as to why they weren't.

This included wanting to continue using, which obviously wouldn't be compatible with treatment, but also fear of judgment or their use being revealed to friends, colleagues or family members, things like that. Also, a lack of awareness of options: as we've talked about, people know about treatment services for opioid use disorder, for example, but the options they have to treat ketamine use aren't widely known. Financial constraints were a big factor in the sort of treatment options people were picking, both in those who were actively seeking treatment and those who weren't, because not many of these options are available on the NHS.

Some people are having to pay out of pocket for treatment and for the treatment options they want, so that's obviously a big factor as to why some people wouldn't be able to get that treatment even if they wanted to. So, three different papers all looking at ketamine use in three very different situations and three very different populations.

Ketamine really has gone from being a niche club drug, or "horse tranquiliser" meme, to something that now has legitimate medical use in therapy, with encouraging results coming out of some of these studies. But as you say, we're also seeing this rise in use, particularly amongst young people. Whether that is self-treatment for depression or straightforward recreational use, there has been this growing acceptance of

ketamine use, hasn't there? It's become more popular and more mainstream, and as a result we're seeing a lot more people, as the third paper showed, needing treatment and experiencing some really quite severe negative effects.

We shouldn't underplay the bladder issues, should we? They are genuinely severe, with some people requiring surgery and having debilitating consequences from chronic ketamine use. I want to touch on that a little bit. We think it's caused by ketamine metabolites causing inflammation of the bladder, potentially even crystallising. I'm not sure we know the exact mechanism, but chronic ketamine use has been associated with these bladder problems for quite a while now, and it does seem to be becoming more prevalent. We're seeing more cases of people who have chronic bladder issues secondary to ketamine.

I guess the question is: are we, as a society, on the one hand promoting ketamine use, and is that leading to this rise in negative effects? And are we pushing down one avenue more than another? Should we be investing more in treatment? I think with ketamine being used off-label as a way of treating treatment-resistant depression, more people who suffer with mental health issues are going to be curious as to whether it can help them and may then go out and use it recreationally as a way of trying to combat their symptoms. But I don't think it's widely known, or widely enough known, what all the negative side effects of ketamine use are. As with any drug, it's always going to come with risks and negative effects, and if we don't talk about it and make people aware of it then people aren't able to weigh up the risks and benefits of their use.

Yeah, I think that's fair. This is where we need longer-term studies on ketamine infusion therapy, don't we? Realistically, though, that ketamine infusion therapy involved giving people 40 or 50 milligrams, whereas some of the people presenting for treatment are using two grams a day, up to 20 grams a day. So there clearly is a difference in dosage between those treatment sessions and what people are using when they've got free access.

Yeah, on the street. I do think the question of treatment services is interesting. Historically, the public health crisis within addiction has been alcohol and opioids generally, and suddenly we've got this new class of drug that's becoming more of an issue as people are now starting to present for treatment. I think there probably does need to be a move within the addiction service community, and I know a lot of my colleagues are working towards that. They're certainly seeing a lot more patients now presenting with ketamine use disorder.

And I think it's also important that when people present to a GP with symptoms like K cramps and bladder issues, healthcare professionals are aware that ketamine could be a potential cause and can help not just with the physical symptoms but also with signposting to addiction services, because that's where you get access to help.

Yeah, that's a really good point. A lot of our addiction colleagues are aware of this rise in ketamine use, but it might well be that GPs, who are the first-line people seeing these patients seeking help, may be much less aware than some of our specialists in the field.

That's a fair point. It's tricky, isn't it? There clearly is a rising public health issue here. I know the government have asked for evidence to consider reclassifying ketamine from a Class B drug to a Class A drug. I don't know what the outcome of that will be, and I'm not sure what difference that will make. It will clearly place more control on ketamine in general.

I did want to talk a little bit about ketamine analogues because this is a pattern we've been seeing with a lot of other drugs. We've talked a lot on here about novel opioids and novel benzodiazepines, and there are ketamine analogues out there as well. Methoxetamine was a compound that was around many years ago and was originally touted as being more bladder-safe than ketamine. There are a few others, such as 2-fluorodeschloroketamine, and a few other compounds that are all very similar in structure. I guess the question is: if we do put stricter controls on ketamine, are we just going to move towards one of these analogues? And the evidence from methoxetamine, at least, was that it wasn't more bladder-friendly and it still caused some of the bladder issues.

I think with anything, once you control one thing there's always a real risk of other things popping up, so if it does get reclassified there is a real chance we might see different variations on ketamine, and what sort of long-term effect they have we just don't know.

Okay, so I think really, in summary, ketamine is showing promise as an antidepressant, but ketamine is also showing significant risk of harm, and I'm not really sure our health services are ready for the potential wave of ketamine use disorder that might be coming their way.

So I think we're going to wrap it up here. I do hope you've enjoyed listening this week. If you want to stay up to date on our latest episodes, do follow us on social media or follow us on Spotify or any of the other platforms, it'd be really appreciated. You can find us on Instagram at @the_tox_lab. As I said at the beginning, we also have a LinkedIn page, and you can also find us on Twitter. If you don't use social media but have any feedback or suggestions for future episodes, you can email us at thetoxlab@gmail.com. We'd love to hear from you. And as always, the papers that we've talked about in this episode will be linked in the description down below if you want to go and check them out and do some reading for yourself. Hope you all have an amazing week, and we'll see you next time. Bye.