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## Ketamine to Treat Alcoholism?

### POSSIBLE USE OF KETAMINE TO TREAT ADDICTION

Ketamine is a schedule-free drug with a long history as an anesthetic. It is also a well-known club drugs on the party circuit. How can it be that it has anti-addictive properties and might be useful to treat alcoholism?

Welcome to the Clinician's Roundtable. I am Dr. Leslie Lundt and with me today is Dr. Stephen Ross. Dr. Ross is the Director of the Division of Alcoholism and Drug Abuse at Bellevue Hospital as well as the Associate Director for Addiction Fellowship Training and is Assistant Professor of Psychiatry at NYU School of Medicine.

#### DR. LESLIE LUNDT:

Welcome to ReachMD Steve.

**DR. STEPHEN ROSS:**

Thank you Leslie. Thank you for having me.

**DR. LESLIE LUNDT:**

Ketamine appears to be a contradiction. Here it's a drug of abuse and a treatment of abusers? Well, we start with the background, Steve. Has it really been around for more than 40 years?

**DR. STEPHEN ROSS:**

It has. It was first synthesized in 1962 by the American chemist, Calvin Steven, at the University of Michigan and actually at that time when PCP was actually available as an anesthetic and during this period, PCP was found to be too psychotogenic that patients would wake up and be forwardly psychotic and they were looking for something that was less psychotogenic and had a shorter half-life. So, they were able to come up with ketamine in 1966. It was then patented by Park Davis, the pharmaceutical company and then in 1970 it was FDA approved as an anesthetic in children, adults, and the elderly and really has been available since then. In fact, we are actually surprised to hear that and its use is primarily now in clinical settings, in emergency room settings, in kids that break their bones and orthopedic surgeons like to use it.

**DR. LESLIE LUNDT:**

Why do they like it?

**DR. STEPHEN ROSS:**

Well, it is safer in that you don't have to use general anesthesia.

**DR. LESLIE LUNDT:**

Hmmm.

**DR. STEPHEN ROSS:**

And that the children are sensitive at lower doses. They essentially dissociate and so their eyes are wide open and the orthopedic surgeon can sort of do what they need to and their children experience no pain and for some reason, they have a lower likelihood of developing any of the side effects like some of the psychotic phenomena that we see with ketamine.

**DR. LESLIE LUNDT:**

And what is the mechanism of action of ketamine?

**DR. STEPHEN ROSS:**

Ketamine is part of a family of arylcyclohexylamines and it categorized as a dissociative anesthetic, but is also in psychiatry categorized as a hallucinogen and it's actually a true hallucinogen and that it can reproduce all of the symptoms of psychosis, positive symptoms, negative symptoms, cognitive symptoms. Its main mechanism of action is that it blocks the NMDA glutamate receptor that is one of the ionotropic glutamate receptors and that mediates its dissociative psychotogenic, analgesic, and psychospiritual effects. But in addition, ketamine is sort of a dirty drug and that it has other mechanisms as well. It has opiate-like effects. It affects the new receptor. It has stimulant-like properties. It is a sum of actually quoted as saying that it has alcohol-like intoxication, cocaine-like stimulation, opiate-like calming, and cannabis-like imaginary. So, actually it has multiple neuropharmacologic effects.

**DR. LESLIE LUNDT:**

So I presume that's what people are after with the high as psychedelic kind of high?

**DR. STEPHEN ROSS:**

You know interestingly, it started in the 90s. It became available as a club drug. I mean actually ever since it was introduced there were reports of abuse. Starting in the early 70s, it was linked with intellectual hedonism and then in the 80s, we saw healthcare workers starting to get addicted. In mid of the 90s, this sort of phenomena of it being included in club-like settings and the users really are looking forward, sort of a psychospiritual, psychedelic properties and they like the fact that it is so short acting that its onset is in about 10 minutes and it's over in about an hour.

**DR. LESLIE LUNDT:**

So, really quick.

**DR. STEPHEN ROSS:**

It's a pretty quick acting drug, yes.

**DR. LESLIE LUNDT:**

And how do they do it? Do they smoke it, shoot it, snort it.

**DR. STEPHEN ROSS:**

They can do all of them. The most common at clubs is they do bumps of it, meaning they will snort it, but you can also inject ketamine intramuscularly and even shoot it IV, but the most common, I would say, is snorting. Actually, you can even smoke it as well.

**DR. LESLIE LUNDT:**

Ketamine has been looked at as an antidepressant, right?

**DR. STEPHEN ROSS:**

That's correct. In fact within psychiatry, that's where you really will see it a lot now, starting with John Crystal's research for Yale, who has looked at the ketamine to help elucidate the NMDA antagonist hypothesis, of schizophrenia and he was interested in blocking the NMDA receptor and how it relates to psychotic symptoms and as a serendipitous find in his research some of the participants reported acute reductions in depression and this really led to ground work. There has now been a couple randomized control studies that have looked at this one by Carlos Zarate at IMH and a couple other people and ketamine is the only agent we know that can effect acute reduction in depressive symptoms of patients with major depression and it appears that about 60% of people with major depression respond with 1 dose 1 time and it can last up to 2 weeks. So, there is a lot of excitement now about how ketamine might be able to help us take a look at the biological bases of depression and it really seems to be a truly noble psychopharmacologic effect with depression and probably it's most promising future indication.

**DR. LESLIE LUNDT:**

So, Steve how might ketamine be useful to treat addiction and it seems so counterintuitive that a drug that makes you high could possibly keep you from getting high or from using anyway.

**DR. STEPHEN ROSS:**

It's a real sort of interesting dilemma because we know ketamine is addictive, we know that it lights up the parts of your brain such as the nucleus accumbens that mediate reward and addiction. We know it increases dopamine transmission in the vital reward-related areas such as the ventral tegmental area and the nucleus accumbens. So, it's interesting that there is research from Dr. Evgeny Krupitsky, who is from Russia who started in 1985, developed a technique using ketamine called ketamine psychedelic psychotherapy and from 1985 to 2002 until ketamine was made illegal and banned in Russia, he treated over 1000 alcoholics and then heroin addicts with ketamine and had some pretty interesting findings. So, in 1 study in the 1990s, he gave ketamine as a 1-time dose to alcohol-dependent patients in addition to their standard, you know, psychotherapy and other treatment for addiction and compared them to the control group that was getting treatment as usual in the clinic and found that 66% of the ones who got the 1-time ketamine those integrated into a meaning-oriented type of psychotherapy were sober at 1 year and the control group 24% was sober and then he followed this up with a double-blind placebo-controlled trial on heroin dependent patients where he gave 2 mg/kg IM of ketamine once versus 0.2 mg/kg as the active placebo and there were 35 patients in each arm and the 1-time dose all the way up to 2 years there was a significant difference in abstinent rates between the experimental group and the placebo and even at 2 years, 18% of the experimental group were sober versus 2% of the controlled group and so, you know, even though these numbers are relatively small, he, you know, has treated many other people and has more experience. So, it is interesting to see how, you know, we just think why would ketamine potentially have anti-addictive properties. Now, it is sort of an interesting thing for me to think about.

**DR. LESLIE LUNDT:**

Hmmm.

**DR. STEPHEN ROSS:**

And so one thing would be to look at the biologic properties of ketamine and in particular the NMDA

receptor. There are other NMDA antagonist that have anti-addictive properties, memantine is an example, the Alzheimer drugs, the acamprosate is another example. A drug called ibogaine, actually it is not available ibogaine, but it is something that is used in Africa and is available to treat opiate addiction. So, one theory may be that it's placing or restoring the tone of the NMDA receptor that has become deficient in alcohol dependence, especially in withdrawal states and going back to why it might helpful in opiates because it is a new opiate antagonist, there is 1 possibility there as well. Other possibilities have to do with altering glutamate transmission. Glutamate is really emerging as a neurotransmitter that is abnormal in the addicted state, that its hyper-glutamatergic responses to drug cues hypo-glutamatergic responses to biologically oriented ones. So, people are looking at how to alter glutamate and the very interesting thing about ketamine is even though it blocks the NMDA receptor, there is some evidence that it actually may increase glutamate function by blocking GABAergic receptors that are normal inhibitory glutamate ones. Although, this speculative has led some to think that blocking the NMDA receptor is what mediates the anti-addictive properties and the parts of it did lead to hyper-glutamatergic responses and other glutamate receptors might mediate its addictive liability. Again, quite speculative, that's the biologic side of things. Now, some would say it helps in addiction because it makes depression better, that it's an indirect response and there is, you know, some data to suggest this and then to me the part of it that is very interesting is that the survey pronounced psychospiritual effects. Ketamine can induce unlike other NMDA, the other NMDA antagonists that I mentioned like the acamprosate and memantine. Ketamine can induce these very profound mystical, spiritual states where people have the sense of experiencing psychological, you know, death of the ego, rebirth of their ego, they have near-death experiences, they can have emotionally intense visions, dream-like states, they can have enhance sense of meaning of things, greater capacity for insight, change in percepts or how they, you know, and see the world and these mystical states where they still feel connected to the Universe, to God, and there is something about the states that have the ability to transform people and we see this in the addiction world where we are used to thinking of spirituality is a vehicle for treatment and conversion to sober state. So, it's interesting to think that it may be the induction of the spiritual state that leads someone to have certain insights that lead into sobriety.

**DR. LESLIE LUNDT:**

After just 1 dose.

**DR. STEPHEN ROSS:**

It seems impossible and 1 thing about the Krupitsky study is he does not say exactly what kind of addiction treatment they get afterwards and it would seem to me that 1 dose would be unlikely, but we hear people, you know you treat enough addicts, they will tell you about a very significant incident in an almost dying from drugs or some other kind of very powerful transformative event that, you know, change them forever. So, it's possible that if the experience is intense enough may be it changes people, but more likely that it may lead to a change in behavior for a period of time and then it may be that if this ever were to be become available to treatment, it will need to follow like an ECT kind of model where you have to dose it repeatedly to integrate the experience to have booster sessions if it were to be sound helpful.

**DR. LESLIE LUNDT:**

Well, thank you so much for being on our show today.

**DR. STEPHEN ROSS:**

My pleasure, thank you for having me.

**DR. LESLIE LUNDT:**

We have been speaking with Dr. Stephen Ross at NYU about the possible use of ketamine to treat addiction.

**I am Dr. Leslie Lundt. You are listening to ReachMD, The Channel for Medical Professionals. For a complete program guide and downloadable podcasts, visit our website at [www.reachmd.com](http://www.reachmd.com). For comments and questions, call us toll free at (888 MD-XM157). Thank you for listening.**

