Episode 030: Ketamine and Psychedelics with Dr. Michael Cummings

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On this week's episode of the podcast, I interview Dr. Cummings, a reputable psychopharmacologist, about ketamine. We talk about psychedelics, the research behind it, both the positives and the negatives. We will look at how it is or is not helpful in psychiatric treatments.

(Disclaimer: There are no conflicts of interest to report. Neither Dr. Puder or Cummings is affiliated with any companies in favor of ketamine and other drug companies.)

Ketamine

Although ketamine has recently become a medication of great interest in psychiatry, it actually is a fairly old medication. It was first synthesized in 1962 and began human trials for anesthesia in 1964. It was finally approved by the FDA as a dissociative anesthetic in 1970.

What has piqued interest in psychiatry is that infusion of a smaller dose of ketamine produces a rapid response in terms of reversal of depressed mood, suicidality, and some treatment-resistant depressed patients.

The literature is rich (in one sense) as the most recent consensus statement (Sanacora, 2017) looked at seven randomized controlled trials, all of which support a robust antidepressant response and anti-suicide response. The difficulty with those trials is the majority of them lasted only one week. A few of the later trials lasted two to three weeks with two to three infusions per week. So, what's lacking at this point is adequate data regarding long term treatment response and data about transitions to more traditional antidepressant treatments.

This area is of great interest, largely because of the limitations of our current antidepressants. In the STAR D antidepressant trials, 48.6% of people got a 50%

reduction in depressive signs and symptoms with the first antidepressant, whereas only 37% of depressed patients achieved remission with the first medication.

Limitations of Ketamine in Psychiatry

People receive low-dose infusions of ketamine for depression and suicidality, and there seems to be short term response to this, though the long term effects have not been measured.

The decrease in depression and suicidality is typically robust, but short lived. There is a fairly rapid decay of the antidepressant response following infusion. The infusions are done over 40 minutes. About thirty percent of the patients will become fairly unresponsive to light verbal stimulation. They then recover, but within a few days their mood will begin to deteriorate.

The study comparing 2 days/week to 3 days/week showed fairly equivalent effectiveness of ketamine for the several weeks it was studied. The other limitation of ketamine in terms of an ongoing treatment for depression is like all NMDA antagonists, these drugs are psychotomimetic and cause dissociation. They can induce psychotic signs and symptoms, and those do begin to become more prevalent with repeated infusions.

Currently adverse effects are known for chronic abusers, and can include cognition problems and bladder issues and we don't have adequate data telling us how long it would be safe to continue ketamine infusions and how to make a transition from ketamine to a more stable, longer lasting treatment.

Ketamine and Dissociative States

Those who described their experiences during the ketamine infusion note a loss of sense of personal boundaries and a sense of union with the universe. There are fairly dramatic changes in their thinking.

Ketamine inhibits the brain's primary activating receptor, the N-methyl-D-aspartatic receptor, blocking the effects of glutamate, which transiently enhances plasticity.

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Ketamine blocks presymptic inhibitor interneurons, blocking glutamate, leading to more glutamate overall in the brain. This “glutamate surge” leads is what is thought to lead to a rapid release of BDNF which is a growth factor for the brain. This may be responsible for the short term improvement in depressive symptoms.

People also use ketamine as a recreational drug because of its ability to induce a dissociative state. It has been a drug of abuse for a number of years since its introduction in the 1970s. It goes by “Special K,” and a number of other names. Many people abuse it after drinking and at raves. If they take a high enough dose, they can lose their ability to hear and see and become stuck in a “frozen state.”

It can produce delirium, which can be either stuporous or agitated. The related drug, phencyclidine (PCP, aka angel dust), causes more severe dissociation and psychosis. However, the effect of ketamine and phencyclidine are in the same direction and by the same mechanism.

People refer to Ketamine’s dissociative state as the “K Hole,” when one can’t move and experiences this depersonalization. Ketamine is sometimes used as a “date rape drug” because the person can be in a very vulnerable state.

Ketamine Dosage

- Ketamine dosage given for depression is at 0.5 mg/kg, which results in a plasma concentration of approximately 70-200 ng/mL.
- Ketamine dosage given for anesthesia results in plasma concentrations of 2000-3000 ng/mL.
- Doses people use at raves or for anesthesia are about an order of magnitude higher than those used for infusion for treatment of depression.
- Peak plasma concentration with antidepressant infusions of ketamine are about 200 ng/mL. For recreational or ICU anesthesia purposes, it is closer to 2000 ng/mL.

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Side Effects/Risks of Ketamine Infusion

When people are recovering from the antidepressant infusion, there is still a risk. They may become agitated, confused, or hallucinate, which is why one of the recommendations for treatment centers using ketamine is that they have adequate expertise in controlling psychomotor agitation and confusion if those things occur.

During ketamine infusion, about one-third of patients also exhibit a fairly pronounced sympathetic arousal during the initial portion of the infusion.

- About 30% of patients achieve a heart rate of 110 and a blood pressure of approximately 180/100. (Sanacora, 2017)
- One of the recommendations for ketamine infusion centers is that they take a good cardiac history and be sure that the person can tolerate exercise. Additionally, the drug should be administered by someone who is ACLS certified and has access to a crash cart.
- For cats recovering from surgery (Jasani, 2015) on ketamine use for animals), it is helpful and ideal to put them in a quiet environment. The same is true for humans. Patients should be put in a quiet, safe environment so that one does not induce an agitated delirium because the patient is responsive to the environment, but their interpretation of that environment may not be based on reality and can produce an agitated response.

Mechanism of Action

In many cases of treatment-resistant depression, it is necessary to alter the plasticity of the brain to get a response. Ketamine, perhaps via the blockade of glutamate at NMDA receptors, and perhaps via downstream mechanisms from that, seems to do this.

This correlates to some extent with how we know antidepressants and electroconvulsive therapy works. They have looked at **CT** scans for what is important in gaining a response, and for decades, it was thought that it was the seizure. Now, it may actually

be the postictal neuronal suppression period that accounts for the therapeutic benefit because that is associated with turning on rapid response genes.

One small study looked at simply exposing people repeatedly to isoflurane, an anesthetic agent, causing repeated neuronal suppression. They also received an antidepressant response from that. So it may be that turning neurons off transiently can be beneficial in terms of resetting them at the DNA level and making them more plastic. Ketamine may not be the only anesthetic agent that alters longer term functioning of neural circuits.

Ketamine Clinics

Although ketamine has become popular, the major risk is not that the drug may not have psychiatric utility, but that we are still fairly early on in using it. The risk is that the use will outrun the data we have available to guide us. This may already be happening, as evidenced by the surge of new ketamine clinics.

Often, the clinics are started by anesthesiologists, and there is no clear psychiatric evaluation that may precede patients starting ketamine.

Currently, the data we have now essentially points to ketamine as treatment for major depression, refractory to other treatments. In many ketamine clinics, they're using it to treat all complaints, but the data on this ranges from slim to none at all.

There may be a lucrative pull toward these clinics as they are usually cash pay since insurances don't currently cover this.

Advice to Those Considering Ketamine Clinics

One should first get a very careful psychiatric evaluation, including a diagnosis of their mental disorder and a careful review of their treatment history to be sure that they have received optimal treatment in terms of established long term treatment options.

If one does decide to pursue ketamine treatment, then they should work with a psychiatrist who is well-versed in not only using ketamine, but is also knowledgeable in

using other means to address depression, such as more traditional antidepressant medications and psychotherapies (especially day treatment programs).

Other Concerns with Ketamine

According to existing literature, ketamine is not a cure all for major depression. It may help "jolt" a brain that has become resistant to treatment into being more plastic and transiently being less depressed, but it is not a cure for the underlying condition.

Another concern is that we don't know what the patient will be like after long-term treatment with ketamine. Will they have had a full recovery? Experience persistent issues or treatment complications? Cognitive issues? Bladder issues?

Ketamine may be most helpful for patients who have failed multiple treatment modalities, such as full doses of antidepressants or even ECT. It may provide a means to enhance treatment response to get the person out of the immediate danger of severe depression and suicidality. However, at this point it is not a standalone treatment.

Ketamine and Psychotherapy

If ketamine is a dissociative drug, it might be best to have the person off of ketamine before starting psychotherapy so that their brain is fully functional. The psychotherapy would need to follow after the person's dissociation has dissipated. The half life of the parent compound of ketamine is about 2.5 to 3 hours. The active metabolite (norketamine or N-desmethylketamine) is up to 12 hours.

By the time the person is 60 hours post-infusion, the ketamine is gone. It is unlikely that there are prolonged dissociative effects, at least not with one, two, or three exposures. However, there is no data stating just exactly how many exposures to ketamine is considered safe in terms of avoiding a more protracted delirium.

Final Thoughts on Ketamine

This is still a new frontier that will most likely be revisited as newer and larger studies are done. Ketamine is promising in that it does suggest that if we can discover more

useful and somewhat more gentle NMDA antagonists, we may discover a new avenue into treating more resistant depressive illnesses.

Psychedelics

History of Psychedelics

Psychedelics are illegal is most areas of the world. Because of a few studies and their ability to alter mental states, they are a gaining interest in some areas of psychiatry.

They have been used for millennia in some Native American and other indigenous populations. Historically, they have been used primarily in terms of religious rituals, often under the guidance of a shaman or medicine man helping to guide an individual in respect to life issues. Traditionally, they were often used only once or very sparingly as a support to what were ritual-based psychotherapies. The interest in psychiatry is if these would facilitate some form of psychotherapy while using the psychedelics.

All of these drugs, such as psilocybin, LSD, and ayahuasca, are all essentially very potent 5-HT2A serotonin agonists, with many of them also being agonists at other serotonin receptors.

They produce a state similar to ketamine.

- The person has an alteration of their sense of self, a loss of boundaries.
- They have a sense of being in touch with the universe.
- They become much more influenceable under those circumstances.

Of course, like ketamine, psychedelics have also been prone to being drugs of abuse like the psychedelic area of the late 1960s. Studies (Kalasinsky, 2014; Palamar, 2016) of people who have used street ecstasy have found that the drug was often mixed with other chemicals, such as methamphetamines and bath salts, making it very different than what could potentially be given at a pharmaceutical grade.

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Psychedelics Dosage

Psychedelics in High Doses

Much has to do with the dosing and concentration that is present when abused, which are often both very high. These drugs can cause permanent changes. For example, LSD can induce a persistent hallucinosis that's essentially the result of a permanent change in receptor status that usually occurred with repeated, very high dose exposures.

Psychedelics in Modest Doses

Frankly at this point, we don't know very easily how to separate the benefits and risks of these drugs. Although used as they were traditionally, there were often very limited exposures and very controlled environments. This suggests that these drugs should perhaps be used with caution for therapeutic benefits.

Studies about Psychedelics (Rafael, 2018 for Most Recent Review)

- Psychedelics have shown benefits in a variety of open label, small studies, and lack adequate control group of mostly short duration for everything from depression, to anxiety, and to even inhibiting the use of substances like alcohol.
- Psilocybin has been studied in decreasing depression in cancer patients
- Patients will take the medication or placebo, wear an eye covering, and listen to some light music while lying down on the hospital bed. If patients do undergo an experience of some sort, there is a person in the room they can talk to.

Most studies typically report a positive primary result, but are limited by their very small samples and lack an adequate control group. Therefore, much of our data is still very early on with respect to the hallucinogens and their possible benefits.

In contrast, the wealth of data from traditional cultures that have used these substances for millennia shows that when these drugs are used in a very controlled, limited manner, they do not seem to induce ongoing mental disorders.

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Research is still at an early stage and may open new routes for treatment by modulation of serotonin receptors in ways that we haven't approached before. It may turn out that hallucinogens themselves may or may not be the right agents to use in the long run. But, this may point to a new approach to altering brain plasticity to enhancing treatment.

Study Designs and Placebos Affect Study Results.

Some studies use saline or sugar pills as placebo, and patients are likely to know they have not received the treatment in those cases. A good placebo produces some degree of change and level of consciousness. For example, an infused benzodiazepine might be a possibility.

A normal saline infusion or an oral sugar pill would not produce an adequately blinded study since both hallucinogens and ketamine produce a fairly rapid effect that anyone being exposed to the drug would be aware of.

Another example is a study that used botox for depression **(Finzi, 2014). 75% of the** Patients knew if they have actually received the botox or just an injection of normal saline since the effects on the muscle were so different. These studies would then become suspect because particularly in treating mood disorders, the placebo response rate is typically fairly high, often around 30-40%. Therefore, studies really do need to blind both the participants and the researchers by giving an active comparative placebo.

The Hawthorne effect can bias the study because if you expect something to happen, you tend to see it, whether it actually exists or not. However, the results of a study can change once it becomes a multi-site study.

Open label studies have a higher rate of positive findings than those of randomized controlled trials.

- In an open label trial, the patient and the prescriber of the treatment both know what the patient is receiving and consequently, they can be biased by their beliefs.

- If you compare open label studies to studies in which neither the patient or the prescriber knows what the patient got, the rate of positive results is about twice in the open trials than what it is in the controlled trial.
    - We can fool ourselves into seeing something that wasn't actually there about half the time.

Final Thoughts

Longer trials of up to six months should be done for ketamine research to address several questions.

- How often can a patient receive treatment?
- What are the long-term effects?
- What is the point at which one should stop because of any long-term effects on a person's brain?
- How do we transition from ketamine infusion to alternative treatments?
- Does ketamine ultimately make the person more responsive to other pharmacologic interventions or psychotherapeutic interventions?

Psychedelics also still need to be studied more extensively.

- We need to understand more fully what is happening in the brain as a result of very potent stimulation of 5-HT receptors.
- Perhaps we can use that as a jumping off point to look for other means to modulate or encourage treatment response using those receptor systems.

We do not know enough about ketamine and psychedelics to be able to tell if they will have positive long term effects on mental health and be useful to psychiatry. These topics will need to be revisited as more research is done.

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