Expert urges cautious approach to ketamine use

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Physicians and patients are excited about ketamine, the latest drug to treat depression, but Stanford psychiatrist Alan Schatzberg says we need to tread carefully.

Ketamine is commonly used in anesthesiology and for severe pain relief. After a number of positive reports in the medical literature, ketamine became more widely used in existing pain clinics, as well as in new ketamine clinics, which started popping up around the country. Patients eager to lift the fog of depression often pay thousands of dollars—insurance rarely pays for the treatment—to lie in a chair while ketamine infuses into their veins. Many of them are trying the drug, still considered experimental, because the most commonly prescribed antidepressant medications have failed to help.

Recently, the FDA approved esketamine, a molecule that is a mirror image of ketamine, as a nasal spray. In this easily administered form, a greater number of patients are likely to seek the drug, which acts much more rapidly than the more commonly used selective serotonin reuptake inhibitors.

Alan Schatzberg, MD, the Kenneth T. Norris Jr. Professor in Psychiatry and Behavioral Sciences, wrote a commentary published online May 21 in the *American Journal of Psychiatry* in which he asked the psychiatric community to proceed with caution when it comes to the new drug. He spoke recently with science writer Mandy Erickson about the dangers and unknowns of ketamine and esketamine.

1. When and how did ketamine and its derivatives first make an appearance in psychiatry?

Schatzberg: Ketamine was first created in 1962 and has been used as a surgical anesthetic since 1970. Its use in psychiatry began in the mid-1990s when researchers studied its role in schizophrenia, as it appeared to induce psychosis. The first report to show its effect on depression was in 2000, when a Yale study indicated that in seven study participants, ketamine was reported to have an effect on mood. Then, in

2006, a study from the National Institute of Mental Health showed that ketamine reduced depression more rapidly than placebo.

2. Why is ketamine receiving so much attention lately?

Schatzberg: Intravenous ketamine has garnered much attention because small doses produce rapid relief—in as little as four hours—in some patients who suffer from treatment-resistant depression. In contrast, it usually takes weeks for patients to see any benefits with selective serotonin reuptake inhibitors, the most common form of antidepressants.

Ketamine clinics, in which patients receive the drug intravenously, have been around for several years to treat chronic pain and depression. Now that it's available in nasal spray form, it's easier to administer it.

3. What are your concerns about the initial studies of ketamine?

Schatzberg: The drug has limited positive data, with only one study out of three demonstrating statistical significance over placebo. The difference is small, and it's difficult to blind because it causes a dissociative state—people wig out—so it's clear when someone has received ketamine and when someone has received a placebo. When you can't blind a trial, it raises some real issues as to whether it's as effective as it seems. It's hard to have great confidence in the findings.

In another study, after about 16 weeks, study participants who were moved from esketamine plus an antidepressant to placebo plus antidepressant experienced a relatively rapid recurrence of depression. It was faster than what was seen with other studies in which participants were moved off antidepressants. In addition, there were a few suicides in

studies to date and these suicides have occurred four to 20 days after the last dose. That could reflect some form of dependence on ketamine to maintain a normal mental state.

Also, we don't know what the effects are of using it long term. We really don't know how long to treat people with ketamine.

4. What connections do you see between ketamine and opioids?

Schatzberg: Ketamine acts in part via an opioid mechanism. We can demonstrate an opioid effect in humans because naltrexone, which blocks the effects of opioids, also blocks the antidepressant effects of ketamine. The same has been shown with naloxone, another opiate antagonist, which blocks ketamine's pain effects in rodents.

Ketamine is abused as a drug in many cultures. China has had hundreds of thousands of ketamine addicts. In Australia, they've banned it. There is a problem in Belgium with ketamine abuse.

What cuts down on the use is that ketamine is not a pure euphoriant. There are some noxious effects; people initially feel weird—agitated and confused. But if you use it repetitively, you build a tolerance to it.

5. What do patients need to know before they use ketamine or esketamine?

Schatzberg: They need to be told that it is not clear what is the best way to use the drug in terms of how often and for how long. They need to be forewarned that the drug could produce dependence, particularly with more frequent use, and that they should watch for withdrawal symptoms in the weeks after stopping it. If symptoms recur, it is not clear what to

do, but it is not unlikely that returning to ketamine will start the cycle over again.

More information: Alan F. Schatzberg. A Word to the Wise About Intranasal Esketamine, *American Journal of Psychiatry* (2019). DOI: 10.1176/appi.ajp.2019.19040423

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