Is ketamine an antidepressant, wellness trend or dangerous drug?

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One 10 ml vial of 1000 mg ketamine. Credit: Psychonaught/Wikipedia

When an autopsy revealed that actor Matthew Perry died of "acute

effects of ketamine," it put fresh attention on an ongoing debate in the field of psychiatry: What's the right balance between expanding access to a drug that can treat depression and imposing boundaries to prevent its abuse?

It's a question that needs more attention from regulators and researchers—particularly with an increasingly sprawling network of ketamine clinics in the US. There have also been rising reports of recreational use, including by Silicon Valley CEOs. Elon Musk, for instance, reportedly uses it both to manage his depression and as a party drug.

Used in the right way, ketamine can help people struggling with severe depression. But the drug also carries the potential for abuse, a risk that the beloved Friends star's death brought into focus. Although Perry reportedly had been undergoing ketamine treatment under the care of a doctor, the levels of drug detected in his blood couldn't have come from that supervised use.

There's reason to worry that Perry's death is a symptom of burgeoning ketamine misuse. Researchers last year found that law enforcement seizures of ketamine more than tripled between 2017 and 2022, an indication that more people are using the drug recreationally.

But beyond concerns of abuse, there's reason to worry that some ketamine clinics are taking advantage of people. Some are offering the drug in unproven forms, like daily microdoses or lozenges, conveniently delivered to their doorstep—for easy cash payments, of course. But we don't have much data on the effects of chronic use of the drug in many of the forms people are using.

Currently, the only version of ketamine approved by the Food and Drug Administration to treat depression is Johnson & Johnson's nasal spray

Spravato, or esketamine. And the regulatory agency put strict boundaries on how even that can be used. For example, a patient can only take the nasal spray under the direct supervision of a health care provider, must be monitored for two hours after treatment, and isn't allowed to drive on treatment days.

But here's where things get complicated: Because ketamine has long been approved as an anesthetic, any doctor allowed to prescribe Schedule II substances can offer it "off label" for depression. Some ketamine clinics might offer it intravenously or as a nasal spray, or offer both the off-label drug and esketamine (which is much more expensive, but potentially covered by insurance).

Meanwhile, some telehealth clinics are whipping up more adventurous—and unproven—forms of the drug, like ketamine lozenges. The lozenges are taking advantage of what's known about ketamine being absorbed by mucus membranes in the mouth, "but the reality is that ketamine isn't particularly well absorbed in the intestinal tract," says Richard Shelton, director of the University of Alabama at Birmingham Depression and Suicide Research Center. Shelton has been involved with several studies of ketamine's use in depression.

Telehealth websites suggest the drugs can also help other areas of mental health, but those promises are unproven. And some sellers recommend low-dose daily use, a form that every ketamine researcher told me was useless. There's no evidence that microdosing is effective at treating depression.

Nor do we know the health effects of such chronic, low-level use. Long-term use at higher doses (the type someone abusing the drug might take) is known to cause bladder and memory problems. The bladder issues seem limited to higher doses, but cognition could be affected at lower levels. A recent study in mice suggest chronic, daily use could

permanently alter the circuitry of the brain.

Taken together, corners of the ketamine clinic universe start to feel predatory. The government should be doing much more to rein them in.

The Drug Enforcement Administration did shut down one South Carolina physician's practice after he sent ketamine lozenges to thousands of patients around the country. And the FDA last fall put out a warning about using ketamine off-label.

But researchers like Sam Wilkinson, associate director of the Yale Depression Research Program, think regulators could go further. One step would be to insist ketamine treatments occur in person. "Our nation is still in the throes of the opioid epidemic," Wilkinson says. "I don't think at this point we're ready to go down the road of take-home dosing until we get some really well-defined, high-quality research."

Another idea is a ketamine registry that would at least generate some safety (if not efficacy) data on off-label use. (Currently, anyone taking Spravato must be enrolled in such a registry.)

But the solution isn't as simple as redirecting everyone to legitimate clinics offering Spravato. That drug is very expensive; it's not always covered by insurance; and some patients might not have the ability to regularly travel a long way to a clinic—if they can get an appointment at all.

That makes it all the more important to put real money behind studying other methods of ketamine therapy. So many people are turning to the drug because other treatments haven't worked. It's worth making sure they are getting something safe.