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Ketamine Antidepressant: Breakthrough or Potential Hazard?

By Tan Teck Boon & Nandhakumar Gunasekaran

Synopsis

Millions of people worldwide suffer from depression. Ketamine has emerged in the West as a promising antidepressant. Its use in depression therapy raises important safety and security questions.

Commentary

WITH FANCY street names like *Special K, Vitamin K or Kit Kat*, ketamine is a popular street drug among substance abusers in Asia. Ketamine first appeared on the recreational drug scene in the mid-1970s mainly in the United States when it was discovered that a small dose of the anesthetic induces hallucinations and a sense of disconnect between the body and mind. In 2006, it was further discovered that ketamine could be used off-label to treat severe mood disorders like depression.

As ketamine has already been approved by the US Food and Drug Administration (FDA) for use as an anesthetic, physicians are permitted under US laws to prescribe it for any medical conditions which they believe the drug to be effective against. Depression is one of those medical conditions.

Treatment-resistant Depression

A debilitating disease, depression causes one to feel a deep sense of sadness and hopelessness. According to the World Health Organisation (WHO), more than 300 million people of all ages worldwide suffer from the mental disorder. Standard treatment for depression includes Selective Serotonin Reuptake Inhibitor (SSRI) prescription drugs like Prozac and Zoloft.

These antidepressants work by increasing the levels of serotonin in the brain to alter

patients' dark moods. Helping to regulate one's mood, serotonin is a neurotransmitter that carries signals between different parts of the body for, inter alia, psychological functions.

Yet, in about 30 percent of the cases in so-called treatment-resistant depression (TRD), these SSRI antidepressants are ineffective. Even when they are, it can take weeks or even months before improvement is seen in patients. Yet, with a small ketamine hydrochloride infusion, results are seen within a few hours with two-thirds of TRD patients reporting an improvement in their moods that last up to a week.

Depression is also often associated with suicide. Studies as far back as the 1980s in the US and Europe suggest that 50 to 60 per cent of those who committed suicides may have suffered from depression or related disorders. For those at risk of suicide, recent studies have suggested that ketamine demonstrates potential as a fast-acting treatment.

As one might expect, the apparent efficacy of ketamine in TRD therapy caught the attention of pharmaceutical companies and doctors. Additionally, several private clinics in the US and Australia have sprung up in recent years offering ketamine therapy for TRD patients. Meanwhile, Janssen Pharmaceutica, a subsidiary of Johnson & Johnson, has patented esketamine – a ketamine-derivative nasal spray that will soon become available in the US.

Big Unknowns

Yet, questions remain over the use of ketamine for TRD therapy. Could the widespread use of ketamine turn it into a health hazard?

The first is drug safety. Although the ketamine dose administered during TRD therapy is low (about one-twelfth of an anesthesia dose), it is unclear what side effects frequent infusions of the drug can have over time. Long-term use of ketamine can cause damage to the liver, kidneys and bladder.

Cognitive impairment has also been observed in recreational users of the drug. With that in mind, ketamine infusion for TRD therapy is akin to taking small doses of a powerful anesthesia repeatedly over extended periods – the effects of which remain unknown.

The second is drug addiction. Repeated use of ketamine can lead to drug dependence – a condition whereby users are addicted to the drug. The worst outcome is where TRD patients end up substituting their debilitating mental condition with drug addiction. Take the ongoing opioid epidemic in the US for example.

Patients turn into opioid addicts because physicians prescribe opioids like OxyContin to them for pain management before stopping the prescriptions at the end of the treatment period, forcing them to seek alternatives. Addicted, they simply turn to synthetic opioids or heroin for relief. One should not dismiss the possibility of ketamine use in TRD therapy producing similar results.

The third is the market-readiness of the drug. Ketamine has only been given to a small

(and at $500 per dose, often wealthy) group of TRD patients. Before a drug is ready for the market, it needs to undergo many years of clinical trials often involving thousands of participants. That being the case, it is easy to see why ketamine is not yet ready for extensive use in TRD therapy.

With less than 400 TRD patients having received ketamine in published clinical trials, its efficacy can at best be described as preliminary and more trials are needed before it can be certified ready for the market.

Security Implications

If Janssen's esketamine nasal spray is made commercially available, authorities in countries where ketamine is a controlled substance will have to deal with it crossing their borders through international travellers who may have such drugs in their possession, with or without a prescription.

Conversely, citizens may also acquire these antidepressant nasal sprays when they travel overseas. For countries like Singapore that have scheduled ketamine as a controlled substance, they will have to invest in the kind of sophisticated detection capabilities needed to prevent this ketamine-derivative from being smuggled across sea, air and land checkpoints.

Then there is the potential for misuse since esketamine nasal sprays can be inhaled in large doses to induce a hallucinogenic high. For countries where off-label use of ketamine is legal, the emergence of a new class of ketamine addicts cannot be ruled out, especially if the drug were suddenly made unavailable to TRD patients.

If there is one lesson from the ongoing opioid epidemic in the US, it is that prescription medications can turn out to be the source of a deadly drug problem. Close monitoring of those who use esketamine is therefore crucial.

At this point, the potential for ketamine (and its derivative, esketamine) use in TRD treatment is in its initial stages. In addition, there are major safety and security implications to consider. But sooner or later, authorities around the world will have to address this emerging issue as the party drug gains legitimacy in the West as a quick-acting antidepressant. And the sooner they prepare for it, the less likely they will be caught off-guard.

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