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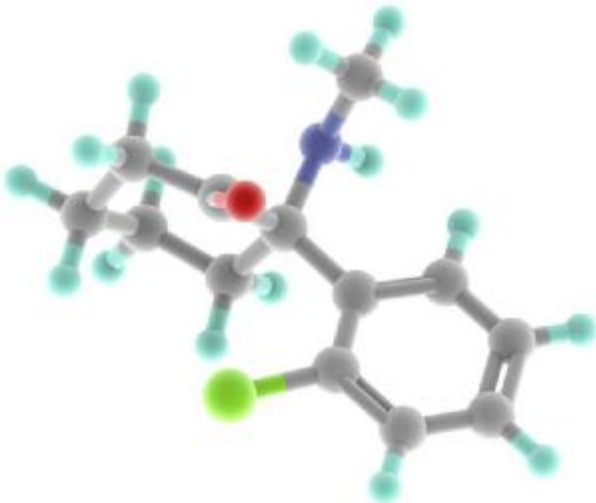
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Researchers Study New Ways to Treat Suicide Risk

The drug ketamine shows promise in early study as doctors work to address the symptoms suicidal patients exhibit



A molecular model of ketamine, a drug that is showing promise in alleviating suicidal thoughts. *PHOTO: PASIEKA/SCIENCE SOURCE*

By **ANDREA PETERSEN**

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Scientists are developing new ways to directly target the suicidal thoughts and behaviors of people at risk.

Researchers are finding that certain medications, like ketamine, clozapine and lithium, may alleviate suicidal thinking. Scientists are also tweaking existing psychological treatments, like cognitive behavioral therapy, and coming up with new ones to combat the desire for self-harm.

When treating suicidal patients, doctors typically address the mental disorders, like anxiety or depression, that often underlie suicidal acts. But that isn't always enough. Treatments, like antidepressant drugs, can take weeks to relieve symptoms—way too long for someone in imminent danger. Patients often have to try several medications to find one that helps. Also, not everyone at risk for suicide has a mental illness.

There's an acute need. Rates of suicide deaths are rising in the U.S. The rate jumped 24% from 1999 to 2014, from 10.5 to 13 per 100,000 people, according to an April 2016 report from the Centers for Disease Control and Prevention.

There's perhaps the most excitement around ketamine. Ketamine has been used in higher doses as an anesthetic for decades. In recent years, it has been studied as a fast-acting treatment for depression, particularly for those whose illnesses haven't responded to other drugs. Ketamine can lift mood in as little as a few hours.

The drug, however, also has short-term side effects including hallucinations and other dissociative feelings. Ketamine is sometimes abused as a street drug known as special K.

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“You might see trails of light, muddled sounds and feel disconnected from your senses,” says Carlos A. Zarate Jr., chief of the section on the neurobiology and treatment of

mood disorders at the intramural research program at National Institute for Mental Health or NIMH. There's some evidence, Dr. Zarate says, that people who have these dissociative symptoms have a better treatment response to ketamine.

In the early depression studies, scientists noticed that the drug alleviated suicidal thinking, too. Newer research is now looking at ketamine's effect directly on suicidal thoughts and behaviors in people at high risk for self-harm.

A small study with no control group published in May in the *Journal of Clinical Psychiatry* followed 14 depressed patients who had experienced suicidal thoughts for at least three months. After six intravenous infusions of ketamine, seven of the patients saw their suicidal thoughts largely disappear. For two patients, the effect lasted three months beyond the treatment. Everyone else, however, relapsed before then.

Dawn F. Ionescu, an assistant professor at Harvard Medical School and the lead author of the study, and colleagues are now working on a larger, placebo-controlled trial of ketamine for suicidal thinking. "The hope would be that ketamine or something like it could eventually be used as a treatment to stop people from progressing to a suicidal act that could lead to death," says Dr. Ionescu, who is also a staff psychiatrist in the depression clinical research program at Massachusetts General Hospital. It could then be added on to treatments for any underlying mental illness.

Researchers at NIMH recently launched a large study to search for so-called biomarkers, like patterns of activity in the brain or levels of stress hormones in the blood, that could help identify people at risk for suicide. The study will also test the effects of ketamine on 50 patients who, within the past two weeks, had a suicide attempt or experienced severe suicidal thoughts.



After decades of struggling with depression and suicidal thoughts, Sarah Kramer, 37, enrolled in a clinical trial of ketamine. She said the drug erased the suicidal thoughts almost immediately. *PHOTO: SARAH KRAMER*

Janssen, a division of Johnson & Johnson, presented results at the Society of Biological Psychiatry scientific meeting in May showing that a version of ketamine, called esketamine, taken intranasally reduced depression symptoms and thoughts of suicide in high-risk depressed patients.

Ketamine acts on the brain's glutamate receptors, which are involved in learning and memory. These receptors interact with the neurotransmitter glutamate, the levels of which seem to be out of balance in depression.

Sarah Kramer has struggled with serious depression and suicidal thoughts since she was a child.

"I have always wished that I did not exist," says Ms. Kramer, now 37 years old, from Medford, Mass. Over the years, she tried various antidepressants, including Prozac and Wellbutrin. Some helped, but only temporarily.

In the summer of 2014, she enrolled in a clinical trial of ketamine at Mass General and received several intravenous infusions of the drug. During the treatment, her vision blurred and she "felt my feet getting further away," she says.

Almost immediately, the suicidal thoughts disappeared. "It was peace and happiness," she says. "I felt I might be able to stick around without it being awful."

After the study treatments ended, she felt well for about a month. But then she declined and the suicidal thoughts returned. Her doctors now prescribe her a version of ketamine taken intranasally. Ms. Kramer takes it every other day. "It is really hard not to abuse it," she says.

There is concern that repeated doses of ketamine could be harmful to the brain. Dr. Zarate and colleagues at NIMH have recently discovered a metabolite of ketamine that they believe could be safer, without the side effects or risk of addiction. Drug companies are also working on their own ketamine alternatives.

Some studies have also found that lithium, a drug commonly prescribed for bipolar disorder, reduces suicidal behavior. Clozapine, an antipsychotic medication often used in schizophrenia, reduces suicidal behavior in those patients. But both medications can have serious side effects.

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