New Hope for Treatment-Resistant Depression: Guessing Right on Ketamine

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I've written in the past about depression – about the devastation depression can cause. It can sap your energy and motivation, disrupt your sleep, appetite, and libido, cause confusion and irritability, and leave you feeling hopeless and worthless. Depression strikes the young, middle-aged, and elderly alike and poses a tremendous burden to individuals, families, and society. And depression can be deadly—raising your risk of death by suicide and a myriad of other medical illnesses. I also wrote about the hope for people with depression. From psychotherapy to medication to brain stimulation therapies, mental health professionals have a number of powerful treatments to offer those suffering from depression.

This spring, people suffering from two particular forms of depression got some welcome news from the Food and Drug Administration (FDA), the agency that approves new medications for clinical use. I wrote previously about how a long history of NIMH-sponsored research led to brexanolone—a revolutionary new medication that acts to rapidly reduce symptoms and restore function to those struggling with the devastating effects of postpartum depression. Brexanolone was approved by the FDA in March 2019.

Also in March 2019, the FDA approved an equally remarkable new medication – esketamine – which targets treatment-resistant depression (TRD). TRD is a form of depression that doesn't get better even after the patient has tried at least two antidepressant therapies. Delivered intranasally in a doctor's office, clinic, or hospital, esketamine acts rapidly – within a couple of hours – to relieve depression symptoms in approximately half patients with TRD. Like brexanolone, esketamine also grew out of a long line of NIMH-sponsored research. The story of how

esketamine came to be, however, is a different one, involving a clever guess and considerable luck, and is equally worth telling. So here goes.

The Guess, or, Enough of Monoamines Already. What About Glutamate?

The possibility that ketamine might be an effective antidepressant started as an educated guess born of frustration. Through the second half of the 20th century, the science of psychopharmacology – the use of drugs to combat the devastating symptoms of mental illnesses – had led a transformation of psychiatry. Effective, cheap, and fast, antidepressant medications became the main weapon in the fight against depression. Each decade or so, a new class of drug was developed, maintaining efficacy with fewer side effects and easier to prescribe and take.

By the 1990s, this rapid pace of incremental improvement slowed dramatically. It turns out, all of the known antidepressants targeted similar mechanisms – increasing the activity of a class of neurotransmitters called monoamines, including serotonin, norepinephrine, and dopamine. Despite many attempts, scientists were unable to improve significantly on the monoaminergic antidepressants, leaving many people suffering from TRD.

Many pharmacologists began to believe that to make significant improvements, new drugs would need to target mechanisms beyond the monoamines. But where to turn? John Krystal, M.D., Ph.D., and Dennis Charney, M.D., at Yale University, made an educated guess: Let's try glutamate. Glutamate is the major excitatory neurotransmitter in the brain, responsible for activating neurons to turn on the key circuits that drive all forms of behavior. Drs. Krystal and Charney had been studying the effects of altering glutamate neurotransmission in healthy subjects and patients with schizophrenia, testing the hypothesis that changes in glutamate function might underly psychosis. They noticed that a particular glutamate receptor blocker, ketamine, had profound psychological effects on people, inducing psychotic-like symptoms. They were aware of preclinical studies, particularly those of Phil Skolnick, Ph.D., D.Sc., and his colleagues suggesting that antagonists of one of the glutamate receptors, the NMDA receptor, had antidepressant-like properties. They also knew that glutamate has important roles in mood, and in the regulation of monoamines. They wondered, might glutamate play a role in depression? Could ketamine be used to treat depression? In a small group of patients with depression, the scientists at Yale found that low doses of ketamine – lower than those that cause psychosis-like symptoms – dramatically reduced depressive symptoms. Remarkably, while monoaminergic antidepressants take weeks to work, the effects of ketamine on depression occurred within hours.

From Ketamine to Esketamine: Proving and Improving

The history of psychopharmacology is unfortunately full of examples of remarkable findings that turn out to be false leads and are not followed through. Not so with the Krystal and Charney findings. Over the two decades since the initial surprising result, numerous careful NIMH-sponsored studies have consistently demonstrated that ketamine rapidly reduces depressive symptoms when given intravenously. Much of this work has been carried out in the NIMH Intramural Research Program (IRP) on the NIH campus in Bethesda, Maryland, where we support about 600 scientists conducting research on everything from basic neuroscience to

clinical trials. After their initial report was published, Dr. Charney joined NIMH as an investigator and recruited Husseini Manji, M.D. and Carlos Zarate, M.D. to build a mood disorders research program in the IRP.

Together, Drs. Charney, Manji, and Zarate planned the first study with ketamine in treatment-resistant depression. In 2006, for the first time in patients, Dr. Zarate and colleagues found that ketamine produced rapid, robust, and relatively sustained antidepressant effects in patients with treatment-resistant depression (in this study, patients had failed over six antidepressants). Since then, among the key findings carried out at NIMH by Dr. Zarate are the findings that ketamine has strong, rapid effects on treatment-resistant depression and bipolar depression, as well as in reducing suicidal thoughts. Furthermore, NIMH and NIMH-funded researchers have conducted a number of studies to better understand the mechanisms by which ketamine may produce these rapid therapeutic effects.

Meanwhile, NIMH-funded scientists around the country, including Dr. Charney, who left NIMH in 2004 to continue his research at the Icahn School of Medicine at Mt. Sinai in New York, carried out additional studies confirming that ketamine was useful in TRD, where it provides relief from depression in about half of patients. Other studies showed that the effects of ketamine last for several days to a few weeks, and that multiple doses can provide continued relief in those who respond.

While these studies convincingly demonstrated ketamine's potential benefits, significant obstacles to its widespread use remained. Most significantly, the intravenous route of administration meant considerable expense and inconvenience to those who might benefit from ketamine. While some physicians began to study intranasal ketamine, Dr. Manji, who had left the IRP to work at Janssen Pharmaceuticals, decided to take a different tack. Like many organic molecules, ketamine consists of two different chemicals that differ only in their 3-dimensional structure: so-called *S*-ketamine and *R*-ketamine. Janssen scientists, working under Dr. Manji, reasoned that *S*-ketamine was the active ingredient, and that if they made a pure form of *S*-ketamine, they could deliver more of the drug to the nasal passages. They manufactured the drug, calling it esketamine. Subsequent clinical trials demonstrated that esketamine, delivered intranasally, had robust antidepressant effects in patients with TRD. Esketamine was granted FDA approval in March 2019.

Building on Success: What's Next in Ketamine Research

The job is not done for TRD. Ketamine and esketamine work, but both have significant drawbacks. Many patients experience uncomfortable dissociative symptoms, hypertension, or other side effects for a few hours after administration. Because of these symptoms, as well as the potential for abuse, both need to be administered in a doctor's office. These aren't medications you can pick up at the pharmacy and take on your own. Dr. Zarate and others are hard at work at finding safer alternatives to ketamine by examining the mechanisms by which it works. One such promising compound, a metabolic product of ketamine, was identified through a collaboration between Dr. Zarate and Todd Gould, Ph.D., of the University of Maryland School of Medicine. A cross-institute collaboration between NIMH, National Institute on Aging, and the National Center for Advancing Translational Science is developing this agent in order to test its efficacy in patients with TRD.

We also need to understand the best ways to utilize the existing drugs. Can ketamine or esketamine be used safely in the long term? Can they be used to reduce the risk of suicide in patients presenting with urgent suicidal thoughts? How can doctors, clinics, and emergency rooms use these medications as a part of a comprehensive approach to treating patients with severe depression and suicidal thoughts or behaviors? These are urgent questions that NIMH-supported research programs seek to answer. But the discovery of the rapid antidepressant capabilities of ketamine has paved the way to asking them – questions we couldn't even have dreamed of back in the 1990s, questions we're only asking because of an educated guess.