Ketamine: A Light in the Darkness

C. ALEXANDER PALEOS, MD
STEPHEN ROSS, MD

KETAMINE HAS BEEN FDA-APPROVED for use as an anesthetic in surgical procedures since 1970,[1] an indication for which it continues to be widely used, especially in disaster relief efforts[2] and battlefield operations.[3] In more recent years, it has been increasingly used for the purposes of conscious sedation and analgesia for painful or anxiety-provoking procedures performed in emergency room settings, particularly in pediatric populations.[4] For almost as long, however, ketamine has been earning notoriety as a drug used illicitly for a variety of non-medical purposes.

Throughout the 1970s, ketamine was used primarily by professionals in biomedical or related fields as a tool for consciousness exploration through the powerful psychedelic states of consciousness it can induce at relatively high doses;[1] this was described by a number of writers in the popular literature of the latter part of that decade, perhaps most famously in John C. Lilly's autobiography, published in 1978. Beginning in the mid-1980s and increasingly in the decades to follow, it gained popularity within the subculture populating nightclubs and dance parties, and later became a fixture, along with MDMA, of the rave scene that flourished in the United States and Europe throughout the 1990s.[1] It is in this context that ketamine obtained its famous street name, "Special K." Its use for recreational purposes has continued unabated to the present day; of late it has become particularly widespread among the youth culture of Asia. For example, a 2012 study reported that ketamine has been the most commonly abused substance amongst teenagers in Hong Kong since 2005.[5]

Since the turn of the century, a third narrative has developed around ketamine, which might ultimately prove to be the most interesting of all: its use as a novel therapeutic agent in the treatment of psychiatric patients suffering from severe, treatment-resistant depression. Unfortunately for the millions of people affected every year by this disease worldwide, with conventional approaches resistance to treatment seems to be the rule rather than the exception. In 2006, the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which followed over 2,800 patients in outpatient treatment for Major Depressive Disorder (MDD) over a period of several years, reported that more than 60% of patients receiving optimized treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram failed to achieve remission of their depressive symptoms; a clinically significant response, let alone remission, was seen in only 48.6%.[6] Of the treatment-resistant patients who then went on to receive the switching or add-on strategies the study was designed to investigate, failure rates ranged from 59% to 83%, with higher treatment resistance seen as more strategies were tried.[6] Furthermore, this finding is not unique to citalopram: Other studies have shown that its efficacy is essentially equivalent with that of any other SSRI and these, if anything, are slightly less effective than older, more poorly tolerated classes of antidepressants.[7]

What the results of the STAR*D study clearly demonstrate is that the current standard of treatment addresses only a subset of depressed patients, and a seeming minority at that. This is perhaps not surprising given the fact that any illness that affects such a broad swath of the population (the WHO estimated in 2004 that 151 million people were affected by unipolar depression worldwide, with another 29.5 million affected by bipolar disorder[8]) is highly likely to represent a final common phenotype for a heterogeneous assortment of underlying disease processes, and the mechanisms by which our current medications work are not heterogeneous enough to address all of them. An analogy has been drawn between this situation and what we understand about the treatment of infectious disease:[9] many

C. Alexander Paleos, MD

Stephen Ross, MD

different organisms cause infections and penicillin, for example, will only succeed in treating some of them. Infectious disease specialists, however, have the luxury of choosing from a variety of different classes of antibiotics, each with its own unique mechanism of action and hence with its own special niche in the arsenal. We psychiatrists, on the other hand, have essentially only one option when it comes to the pharmacologic treatment of depression, and this is to intervene at the level of the monoamine neurotransmitter system, which in the brain consists mainly of serotonin, norepinephrine, and dopamine.

In 1957, Nathan Kline published the first report of a pharmacologic compound demonstrating efficacy as an antidepressant. This was iproniazid, the first monoamine oxidase inhibitor (MAO-I), an anti-tuberculosis medication that itself had been discovered only a few years previously. Its effectiveness as an antidepressant had been discovered serendipitously, initially noted as a side effect of treatment in tuberculosis patients.[10] Its mechanism of action was ultimately determined to be mediated by increasing levels of serotonin, norepinephrine, and dopamine in the brain by inhibiting the enzyme that degrades them. That same year, in Germany, Ronald Kuhn published his findings of the antidepressant effects of another compound, imipramine, the first tricyclic antidepressant[10] and one that continues to be prescribed to this day. He had been testing it to see if it might be effective as an antipsychotic, and though it failed utterly in this regard, he noted, again serendipitously, that some of his depressed schizophrenic patients showed dramatic improvements in their mood symptoms in response to taking it.[10] Its major pharmacologic effect is to increase levels of serotonin and norepinephrine. In 1987, the FDA approval of the first SSRI, fluoxetine (Prozac), ushered in a new era of antidepressant treatment[10] owing to its much safer and better tolerated side effect profile, and the SSRIs continue to dominate the contemporary therapeutic landscape. But again, this class, and its more recent descendants, the selective serotonin-norepinephrine reuptake inhibitors (SNRIs), exert their effect by means of the monoamine system, as their names imply. Since 1957, in fact, every medication approved for use as an antidepressant has acted on one of these three molecules, or some combination thereof.[9]

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This is not to underestimate the impact these medications have had. Unquestionably, they have revolutionized the treatment of depression and, along with the discovery in 1952 of the first antipsychotic, chlorpromazine, revolutionized the entire field of psychiatry. Untold millions of people have benefited from their use and continue to do so. For the patients that do respond to the monoamine-specific antidepressants, the effect can be life-transforming and literally life-saving. But just as penicillin has saved countless millions of lives and was arguably the most im-

portant discovery of the 20th century, there remain vast numbers of people every year who acquire infections for which penicillin is completely ineffective, and for which alternative treatments must be sought. By analogy, this is precisely the problem faced by modern psychiatry where the treatment of depression is concerned. Our one-trick pony is desperately in need of new tricks.

This is where ketamine enters the picture. As a potent antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, one of the brain's two major receptor types for glutamate, ketamine acts on a neurotransmitter system entirely distinct from the pathways involving serotonin, norepinephrine, and dopamine. Glutamate is the major excitatory neurotransmitter for the central nervous system, and its effects are thus manifold and widespread, involving all aspects of the neuronal life cycle, from migration and differentiation, to the genesis of new axons, to the survival of the neuron itself.[11] And while the pathophysiological mechanisms underpinning depression are far from completely understood, there is mounting evidence to suggest that in addition to the monoamines, there is a significant and perhaps central role played by glutamate as well. For example, it has been found that depressed patients have elevated levels of glutamate in their blood and cerebrospinal fluid as compared to healthy controls, and these changes can be reversed by chronic administration of conventional antidepressants.[11] Additionally, postmortem analyses of brain tissue samples have shown significant alterations of the NMDA receptor in the frontal cortex of patients with MDD[12] and in the prefrontal cortex of completed suicides.[13] Taken together, this evidence paints a picture in which treating depression with ketamine, despite its checkered past, starts to make a lot of sense, as surprising as this might be to laypeople and perhaps especially to most psychiatrists, who are accustomed to viewing it primarily as a drug of abuse.

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The earliest reports on the use of ketamine in the treatment of psychiatric conditions date from the 1970s and describe its use as an adjunct to psychotherapy, with some anecdotal evidence for efficacy in reducing symptoms of depression and anxiety.[14] This line of research was evidently not pursued much further, but interest in its potential as an antidepressant resurfaced in the late 1990s on the heels of the abovementioned evidence for the role of glutamate in the pathophysiology of depression, as well as a number of studies using animal models for depression that gave evidence for the effectiveness of NMDA receptor antagonists.[15–17] In 2000, Robert Berman, John Krystal, and their colleagues at Yale University, who had previously been investigating high-dose ketamine as a model for the experimental induction of schizophrenia-like symptoms in healthy volunteers,[18] published the first placebo-controlled study evaluating the use of ketamine as an antidepressant in humans.

In this study,[19] ketamine demonstrated not only a robust antidepressant effect in seven of their eight acutely depressed subjects, with significant improvement on scales measuring mood, suicidal ideation, helplessness, and worthlessness, after only a single intravenous administration of a relatively low dose (roughly 25 to 50% that used for anesthesia), but one that occurred within hours of treatment, and persisted for seven to 14 days. Compare this with the SSRIs, which show no acute antidepressant effect and typically take 6 to 8 *weeks* to achieve full efficacy. The rapidity of the response alone has important implications, especially in cases of severe depression with prominent suicidal ideation, where a rapid resolution of symptoms is highly desirable and potentially preventative of self-harm. Berman's study would prove to become seminal, as it provided, for the first time in humans, evidence for a treatment with effects mediated independently of the monoamine system, showing an antidepressant response markedly different from that seen with conventional medications and, even more importantly, a ray of hope for the many patients who have been failing for years to respond to them.

Nonetheless, this small study initially failed to garner much notice, and another study investigating the use of ketamine for depression would not be published until 2006, when Carlos Zarate, Jr. and his colleagues at the National Institute for Mental Health reported their findings in a group of 18 depressed patients given the same intravenous dose used at Yale.[20] Their findings were impressive: One day following a single IV dose of ketamine, 71% of their subjects showed a response in their depressive symptoms, and 29% achieved full remission, compared to none for placebo. Of the subjects who responded, 50% sustained this response for a week or more. The fact that Zarate's group recruited their subjects on the basis of resistance to conventional antidepressants—all 18 had failed at least two of these prior to entering the study—made their results all the more intriguing.

Since then there has been a tremendous upsurge of interest in evaluating ketamine's antidepressant properties. Over the past seven years, more than 25 publications have appeared in the literature, involving over 160 patients, most with treatment-resistant depression. All of them, with the exception of one isolated case report, have confirmed its efficacy as an antidepressant, consistently showing the same pattern of rapid and relatively prolonged—compared with ketamine's half-life, which is measured in hours—response in symptoms.[21] It has also been shown that ketamine effectively treats the depression seen in both major depressive and bipolar disorder, without exacerbating risk for mania in the latter.[22, 23] There have been no serious adverse events in any of these studies; the side effects that have been reported have been typically mild to moderate in severity, and none have persisted beyond the time of the drug's administration.[21] Among these are feelings of dissociation from reality, as well as so-called psychotomimetic symptoms, such as

visual hallucinations or other perceptual disturbances. Indeed, ketamine's propensity to elicit these symptoms, along with its perceived liability for abuse, has been cited by a number of authors as an argument against its adoption as a standard treatment for depression.[9, 24]

Nevertheless, enthusiasm for its use is only gaining momentum. As of this writing, 25 new studies investigating ketamine in depression are on file at the ClinicalTrials.gov database. Some institutions have already started offering it to the public, outside of a research context, as an off-label treatment for refractory depression. The University of California, San Diego, for example, operates an outpatient clinic devoted to this, with highly positive results reported thus far.[25] This is a trend that is likely only to continue, as the data supporting its safety and efficacy in otherwise difficult or impossible to treat cases of depression continue to multiply. Yet there remain some important unanswered questions, which some of the studies currently underway are intended to address. One of the most important is the question of how to most effectively maintain the antidepressant effect beyond the one to two weeks that is typically seen after the initial dose. One study has already reported on the efficacy of a repeat dosing strategy, which seems promising,[26] and there are others currently underway attempting similar protocols.[27–29] Others are trying strategies involving bridging to daily use of an oral agent, such as a traditional antidepressant[30] or an orally active glutamate release inhibitor.[31] Another important question has to do with optimizing the dose, as most of the studies to date have simply followed the protocol employed in the initial proof-of-concept study. It is not known, however, whether a lower dose would be as effective, and there is at least one study to suggest that it very well could be, with the added benefit of attenuating the undesirable side effects.[32] There are currently two relatively large-scale dose-response studies underway designed to address this issue.[33, 34]

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Regardless of the answers to these lingering questions, it seems clear at this point that ketamine has established itself as a viable, exciting, and long-awaited novel treatment for depression. It is exciting for the new hope it brings to the huge numbers of treatment-refractory patients that continue to suffer from depression's debilitating effects, as well as for the new possibilities it brings for the development of novel treatments down the road. The glutamate system and the role it plays in the etiology of mood disorders is only just now starting to be deciphered, and a new era of treatment appears to be looming on the horizon for psychiatry. For a field that has been groping in the dark for decades in search of more effective ways to alleviate the suffering of those who turn to it for help, this is a welcome ray of sunshine indeed.

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C. Alexander Paleos, MD *obtained his medical degree from the University of Pittsburgh and underwent his residency training in psychiatry at NYU Medical Center and Bellevue Hospital in New York City, where he continues to live and work. Since 2010 he has been involved as a study therapist in the NYU Psilocybin Cancer Anxiety Project, investigating the utility of psilocybin-assisted psychotherapy and psilocybin-facilitated mystical states in the treatment of anxiety and depression in terminally ill cancer patients. His interest in researching novel therapeutics for mood and anxiety disorders has more recently led to his involvement with ketamine, and he and Dr. Stephen Ross are currently collaborating on devising an experimental protocol to investigate its use as a treatment for severe depression and acute suicidality in an emergency room setting. He can be reached at Kosmas.Casey.Paleos@nyumc.org*

Stephen Ross, MD *is Associate Professor of Psychiatry and Child & Adolescent Psychiatry at New York University School of Medicine and Associate Professor of Oral and Maxillofacial Pathology, Radiology, and Medicine at the NYU College of Dentistry. He directs the Division of Alcoholism and Drug Abuse and the Opioid Overdose Prevention Program at Bellevue Hospital Center in New York City. He is Director of Addiction Psychiatry at NYU Tisch Hospital and Director of the NYU Addiction Psychiatry Fellowship. He is an expert on the therapeutic application of serotonergic hallucinogens to treat psychiatric and addictive spectrum illnesses. He directs the NYU Psychedelic Research Group and is Principal Investigator of the NYU Psilocybin Cancer Project. He can be reached at Stephen.Ross@nyumc.org.*