Ketamine: Peril and Promise

R. Andrew Sewell, MD
asewell71@gmail.com

Those following science news will have noticed some recent buzz about ketamine. What's going on?

Carlos Zarate Jr., MD, of the National Institute of Mental Health (NIMH) recently injected 18 patients who had treatment-resistant depression with ketamine and found that their depression significantly improved within hours - an improvement that lasted for up to a week after a single dose.[1] This is in striking contrast to conventional antidepressants, which have to be taken every day and need weeks to months to have any therapeutic effect. The importance of these findings was articulated by the NIMH director, Thomas Insel, MD: "To my knowledge, this is the first report of any medication or other treatment that results in such a pronounced, rapid, prolonged response with a single dose." This study corroborates earlier findings by researchers in 2000 who gave ketamine to seven depressed patients and noted a remarkable and lasting remission of depression in all of them.[2]

Veterans began to return to the United States with unusual stories about psychedelic experiences they had experienced while on the operating table…

By coincidence, Zarate was an attending physician at the medical center where I did my training, and I remember well the dismay everyone expressed when he left for bigger challenges at NIMH, as he was renowned for his excellent clinical skills and teaching ability. Strangely enough, I don't remember his ever expressing an interest in psychedelic drugs!

Given that this is a major positive news story related to psychedelic drugs, it is perhaps worthwhile to step back and see what work has been done with this unusual psychedelic and where we might see ketamine research leading.

What Is Ketamine?

Ketamine is an arylcyclohexylamine, the same class of drugs as dextromethorphan (DXM, "robo") and phencyclidine (PCP, "angel dust") (Figure 1). It was invented in 1962 by the pharmacist Calvin Stevens and patented in 1966 by Parke-Davis for use as an anaesthetic in humans and animals. It is a neurotransmitter antagonist that blocks excitatory glutamate from reaching the N-methyl-D-aspartate (NMDA) receptor. In higher doses, it also stimulates the mu and sigma opiate receptors and increases epinephrine and endorphin levels. It affects primarily the hippocampal formation (responsible for memory) and the prefrontal cortex (responsible for abstract thought), explaining its profound effects on both.

Ketamine saw initial use in army field hospitals in Vietnam – where it was considered useful because it acts quickly, allows rapid recovery, and depresses consciousness without disrupting breathing or circulation, unlike most

Unlike most of the other psychedelic drugs, society never really lost sight of the benefits of ketamine…

anaesthetics. This means that monitoring and support by an anaesthesiologist is not necessary, and a single surgeon can in theory perform an operation unaided.[3] Veterans began to return to the United States with unusual stories about psychedelic experiences they had experienced while on the operating table, however. Similar to LSD, ketamine induces vibrant hallucinations, but unlike LSD, ketamine lasts only an hour or so and induces an "out-of-body" state similar to that of a near-death experience. In 1965, professor Edward Domino coined the term "dissociative anaesthesia" to describe ketamine's trancelike effects.[4] Interest in the psychological effects of the new drug spread rapidly. Karl Jansen, MD, PhD, who devoted his entire career to understanding ketamine from the receptor to the social level, came to believe that ketamine had potent healing powers (see Ketamine: Dreams and Realities, published by MAPS). By the mid-1970s ketamine was being used in Argentina to regress clients "back to the womb,"[5] and psychotherapeutic use continues to this day. This use is even reflected in popular culture. An X-Files episode in 1993 ("Demons") featured Agent Mulder being given ketamine by a rogue doctor in order to help him recover his lost memory.

However, recreational use of ketamine also mushroomed over the same period, together with scare stories in the media. It was immediately dubbed a "date-rape" drug, just as MDMA and GHB had been in turn, despite the fact that the drug most overwhelmingly implicated in rapes is alcohol. Alarm started to grow within the psychedelic community as well, for different reasons. Although psychedelic drugs are generally considered to be nonaddictive, ketamine seemed to be the exception. The American researcher Dr. John Lilly, well versed in other psychedelics such as LSD, found his ketamine use spiralling beyond his control, and he nearly drowned once while under its influence. D.M. Turner, author of The Essential Psychedelics Guide and Salvinorin - the Psychedelic Essence of Salvia Divinorum, also became addicted and was finally found drowned in a bathtub at the age of 34, having succumbed during a ketamine trip. Marcia Moore, who penned one of the first descriptions of the effects of ketamine in her autobiography Journeys Into the Bright World, vanished one night under the influence of ketamine in 1979, and her skeleton was found in a tree two years later.[6] Ketamine slowly acquired a reputation for insidiously trapping those who really knew better. The psychedelic was added to the Drug Enforcement Administration's "emerging drugs" list in 1995, then moved to Schedule III – the same class as buprenorphine and anabolic steroids – in 1999.

Medical Use of Ketamine

Why, given ketamine's evident dangers, was it not put into Schedule I instead? Schedule I is reserved for drugs with "no currently accepted medical use," and the medical uses for ketamine are plentiful. Aside from applications on the battlefield and in veterinary medicine, lower doses also appear to be helpful in managing chronic pain conditions. When pain fibers from an injury site activate, they trigger a chain reaction that changes the structure of the pain neurons themselves. These changes can sometimes provoke the neurons to fire even more, in an out-of-control feedback loop called spinal sensitization, or the "wind-up" phenomenon, that creates even more pain. Unlike most anaesthetics, ketamine's NMDA-receptor (and thus long-term potentiation) blocking effects prevent this sensitization. At doses of 0.1 to 0.5 mg/kg/h, ketamine is useful as a local anaesthetic and as a treatment for chronic pain. It acts synergistically with opioids to further improve pain relief and is particularly useful in treatment of pain that is caused by cancer.[7]

One form of pain resulting from sensitization is called complex regional pain syndrome (CRPS), in which a seemingly minor trauma becomes more painful with time rather than less and is accompanied by changes in the skin and autonomic response in the affected limb. The pain can be severe and is often both chronic and resistant to conventional therapy. In 2002, a team in Germany led by Ralph-Thomas Kiefer, MD, kept six patients with CRPS unconscious with a continuous ketamine infusion for a week and found that four were cured and two

were relieved of their pain for one and three months respectively.[8] Mindful that a week of intensive monitoring in the ICU is seldom a practical treatment for anything, G.E. Correll's group at Penn State Hershey Medical Center reviewed the medical records of 33 patients given low-dose (subhallucinogenic) ketamine for CRPS instead and found that three-quarters had experienced complete pain relief and 31 percent were still pain-free six months later.[9] This was enough to prompt a prospective trial in which 40 patients with CRPS were given subhallucinogenic doses of ketamine. They reported significant pain relief that lasted for weeks in most of the patients and caused a permanent remission in three.[10]

There are also suggestions that ketamine might be useful in the treatment of heroin withdrawal. In one recent study, 58 opiate-dependent patients were given "ultra-rapid detox" under general anaesthesia with either ketamine or placebo saline infusion.[11] The ketamine group had noticeably better control of withdrawal symptoms, although there was no difference in abstinence between the two groups four months later.

More recently, the Department of Defense has become interested in developing an intranasal ketamine spray for battlefield use.[12] Presumably an injured soldier on ketamine is more able to guide a tank to safety than one sedated with morphine!

Finally, a remarkable case of rabies survival mediated by ketamine was reported two years ago in the New England Journal of Medicine.[13] A 15-year-old girl did not report that she had been bitten by a bat until it was already too late. Reasoning that the virus could not multiply in nonfunctioning neurons, Willoughby and his team flatlined her on ketamine for over a week, halting the spread of the virus and giving the girl's immune system time to activate and eliminate the disease, thus saving her life. Initial enthusiasm for this method has been tempered by four subsequent attempts that have not been such resounding successes, however.[14]

Psychotherapeutic Use of Ketamine

During the late 1960s, Lilly conducted initial research with ketamine as an agent to induce nonordinary states of consciousness. He was the first to characterize the relationship between dosage and the nature of the ketamine experience.[15] Jansen has since argued that rather than using ketamine as an adjunct to psychotherapy, in the way that MDMA is typically useful, the altered state induced by ketamine is in itself therapeutic. Its resemblance to a near-death experience can have a similar effect as an actual near-death experience. For example, it can supposedly reduce anxiety about death, increase altruism, and make people less concerned with material goals.

In 1973, the Iranian psychiatrist E. Khorramzadeh, MD, published the first report on the use of ketamine as an adjunct to psychotherapy.[16] His patients reported a number of different effects. Many vividly recalled painful childhood events. "I always desired to make nasty remarks but dared not," said one. "The injection took away the discomfort in my chest," reported another. "My heavy burden of sin is gone now," "I now feel care-free, with no worries," and "As a child I always wanted to shout but they did not let me," were other responses. Ninety-one percent of the patients were still doing well six months later. A later study by the same researcher attempted to predict response to ketamine based on personality type (as measured by an Iranian version of the Eysenck Personality Inventory) and found that pleasant experiences were well-correlated with high "Extraversion" scores, whereas unpleasant trips were had by those with low scores.[17] A decade later, Hanscarl Leuner, MD, one of the earliest pioneers of LSD therapy in Europe and author of the encyclopedic volume Hallucinogens, was using ketamine as a psychotherapeutic agent at his psycholytic treatment center at the University of Gottingen.

Later still, across the Atlantic, a British team found that by combining ketamine (to block long-term potentiation and stimulation of compulsive behavior) with an opioid blocker (to prevent loss of consciousness), patients with refractory

…ketamine might be useful in the treatment of heroin withdrawal.

It is gratifying to see that NIMH is following MAPS' lead in supporting the treatment of psychiatric disorders with psychedelic drugs.

anorexia nervosa completely lost their compulsive thoughts with repeated doses.[18] "The speed with which a person changed from the high arousal, compulsive state to the more normal state was occasionally fast enough to resemble a change in personality," they noted. "This was particularly so with patient 8, whose husband described her as changing back to the personality he knew when he first married her. The patient found the speed of change difficult to adapt to in the first week." More than half of the patients showed a return to normal eating behavior that persisted long after discharge from the hospital.

Ketamine's effects on depression were first noticed by a team led by psychiatrist John Krystal at Yale, who was studying ketamine as a way of understanding schizophrenia by deliberately inducing psychosis. "For many, it was a huge, obvious effect," said Krystal. "One of the patients said, 'Don't give me those old medications, I want this again'." At the time, this was just an incidental finding, however. Because the behavioral effects of ketamine resemble those of schizophrenia and dissociative states, Krystal reasoned that ketamine administration would be an ideal way to study such states, which he then proceeded to do, in both normal controls and schizophrenics, unwittingly illustrating one of the hazards of psychedelic research. Following a blistering expose in the Boston Globe in 1998 alleging irresponsible Nazilike administration of psychedelics to helpless mental patients,[19] some advocacy groups, such as Citizens for Responsible Care in Psychiatry and Research, called for a complete moratorium on such "challenge" studies, and two months later the NIMH responded with a shutdown of Krystal's ketamine research for "lack of scientific merit." Although the subsequent, more sober debate among the scientific community ultimately concluded that his studies were in fact conducted ethically,[20] and they were permitted to continue, albeit in a more cautious fashion, the episode is a sobering reminder of the potential risks of psychedelic research to the researchers themselves, if not the subjects! Krystal's work ultimately led to Zarate's study, which could potentially lead to the world's first rapid-acting antidepressant. Scientific merit is clearly in the eye of the beholder.

But the giant in the field of ketamine psychotherapy is surely Evgeny Krupitsky, MD, PhD, chief of the research laboratory at St. Petersburg Regional Center of Addictions and Psychopharmacology, who has been researching the treatment of alcoholism and addiction with ketamine since the 1980s and hopes to extend his research to encompass post-traumatic stress disorder in the near future.

In 1985, he developed ketamine psychedelic therapy - which was initially merely a method for increasing suggestibility and enhancing aversive treatment for alcoholism - publishing his first report on the method in 1992.[21] He found that ketamine induced total abstinence in 66 percent of his alcoholic patients (versus 24 percent of the nonpsychedelic control group) for as long as a year. He observed improvement in personality profile, positive transformation of self-concept and emotional attitudes to various aspects of self, positive changes in life values, and improved spiritual development in the ketamine group.

What is the contribution of the psychedelic experience to this improvement? Krupitsky posited nine factors:[22]

1. Stable, positive psychological changes.
2. Personality growth and self-cognition.
3. Important insights into existential problems and the meaning of life.
4. Transformation of one's "life value system."
5. A change of view of one's self and the world around.
6. Insight into life and death.
7. A rise of creative energies.
8. Broadening of spiritual horizons.
9. Harmonization of a person's relationships with the world and with other people.

In 1991, another Soviet psychiatrist, Igor Kungurtsev MD, who had initially worked with Krupitsky and later immigrated to the United States, published a summary of his own experiences treating alcoholism with ketamine.[23] Although, like Krupitsky, he initially felt that ketamine simply made alcohol aversive in a purely behavioral way, he radically changed his approach following a series of ketamine self-administrations and instead

adopted a transpersonal model for therapy in order to better utilize the profound mystical experiences induced by ketamine. He found that successful treatment of alcoholism with ketamine was correlated with a changed spiritual outlook in the same way that 12-step programs also achieve success by changing addicts' spiritual outlook, albeit in a nonpsychedelic manner.

MAPS' Support for Ketamine Research

It is gratifying to see that NIMH is following MAPS' lead in supporting the treatment of psychiatric disorders with psychedelic drugs. MAPS has long been a supporter of Krupitsky's work, co-funding (with the Heffter Institute) his recently published study on the treatment of heroin addiction with ketamine.[24] Krupitsky and his team found that heroin-dependent subjects receiving three sessions of ketamine-assisted psychotherapy had over twice the rate of abstinence of those receiving only a single session. This contradicts the notion that psychedelic drugs somehow represent a "magic bullet" or "instant miracle cure" by showing that a single administration of a psychedelic drug is often not fully effective.

Like any powerful drug, ketamine carries with it considerable danger as well as profound potential for benefit. Unlike most of the other psychedelic drugs, society never really lost sight of the benefits of ketamine because its applications in anaesthesia were so obvious. Now the psychological benefits of ketamine at lower doses are becoming apparent also, we can hope to see a renaissance in ketamine research that will translate into increased acceptance for other research with psychedelic drugs as well. •

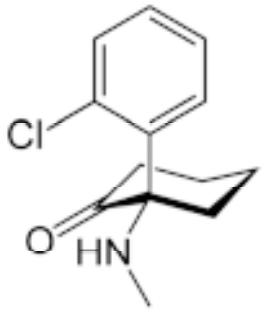

Figure 1: The structure of ketamine

References

1. Zarate CA Jr., Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856-864.

2. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351-354.

3. Bonanno FG. Ketamine in war/tropical surgery (a final tribute to the racemic mixture). Injury 2002;33:323-327.

4. Domino EF, Chodoff P, Corssen G. Pharmacologic Effects of Ci-581, a New Dissociative Anesthetic, in Man. Clin Pharmacol Ther 1965;6:279-291.

5. Mozayani A. Ketamine-Effects on Human Performance and Behavior. Forensic Sci Rev 2002;14:123-131.

6. Kelly K. The Little Book of Ketamine. Berkeley, Calif.: Ronin Publishing, 1999.

7. Saito O, Aoe T, Kozikowski A, Sarva J, Neale JH, Yamamoto T. Ketamine and N-acetylaspartylglutamate peptidase inhibitor exert analgesia in bone cancer pain. Can J Anaesth 2006;53:891-898.

8. Kiefer R, Rohr P, Unertl K, Altemeyer K, Grothusen J, Schwartzman RJ. Recovery from intractable complex regional pain syndrome type I (RSD) under high dose intravenous ketamine-midazolam sedation. Neurology 2002;58A:475.

9. Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med 2004;5:263-275.

10. Goldberg ME, Domsky R, Scaringe D, et al. Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. Pain Physician 2005;8:175-179.

11. Jovaisa T, Laurinenas G, Vosylius S, Sipylaite J, Badaras R, Ivaskevicius J. Effects of ketamine on precipitated opiate withdrawal. Medicina (Kaunas) 2006;42:625-634.

12. Javelin Pharmaceuticals. IDDS Presents Intranasal Ketamine Data at Premier Department of Defense Scientific Meeting [online]. Available at: http://ir.javelinpharmaceuticals.com/releasedetail.cfm?ReleaseID=209623. Accessed March 23.

13. Willoughby RE Jr., Tieves KS, Hoffman GM, et al. Survival after treatment of rabies with induction of coma. N Engl J Med 2005;352:2508-2514.

14. Hemachudha T, Sunsaneewitayakul B, Desudchit T, et al. Failure of therapeutic coma and ketamine for therapy of human rabies. J Neurovirol 2006;12:407-409.

15. Lilly J. The Scientist: A Metaphysical Autobiography. Berkeley: Ronin Publishing Inc., 1997.

16. Khorramazadeh E, AO L. The Use of Ketamine in Psychiatry. Psychosomatic Journal 1973;14:344-346.

17. Khorramazadeh E, Lotfy A. Personality Predisposition and Emergence Phenomena with Ketamine. Psychosomatic Journal 1976;17:94-95.

18. Mills IH, Park GR, Manara AR, Merriman RJ. Treatment of compulsive behaviour in eating disorders with intermittent ketamine infusions. Qjm 1998;91:493-503.

19. Kong D. Drug Studies are Questioned. The Boston Globe 1998 Dec. 31.

20. Carpenter WT Jr. The schizophrenia ketamine challenge study debate. Biol Psychiatry 1999;46:1081-1091.

21. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. J Psychoactive Drugs 1997;29:165-183.

22. Krupitsky EM, Grinenko AY. Psychedelic drugs in psychiatry: Past, present and future. V. M. Bekhterev Review of Psychiatry and Medical Psychology 1992;1:31-47.

23. Kungurtsev I. "Death-Rebirth" Psychotherapy with Ketamine. The Albert Hofmann Foundation Bulletin 1991;2:1-6.

24. Krupitsky EM, Burakov AM, Dunaevsky IV, Romanova TN, Slavina TY, Grinenko AY. Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence. Journal of Psychoactive Drugs March 31, 2007.