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Taming the Ketamine Tiger

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Pharmacologic Effects of CI-581, a New Dissociative Anesthetic, in Man. By E. F. Domino, P. Chodoff, G. Corssen. Clin Pharmacol Ther 1965; 6:279–91. Reprinted by permission from Macmillan Publishers Ltd., copyright 1965.

Abstract: Pharmacologic actions of CI-581, a chemical derivative of phencyclidine, were determined in 20 volunteers from a prison population. The results indicate that this drug is an effective analgesic and anesthetic agent in doses of 1.0 to 2.0 mg per kilogram. With intravenous administration the onset of action is within 1 min and the effects last for about 5 to 10 min, depending on dosage level and individual variation. No tachyphylaxis was evident on repeat doses. Respiratory depression was slight and transient. Hypertension, tachycardia, and psychic changes are undesirable characteristics of the drug. Whether these can be modified by preanesthetic medication was not determined in this study. Recovery from analgesia and coma usually took place within 10 min, although from electroencephalographic evidence it may be assumed that subjects were not completely normal until after 1 to 2 h. No evidence of liver or kidney toxicity was obtained. CI-581 produces pharmacologic effects similar to those reported for phencyclidine, but of shorter duration. The drug deserves further pharmacologic and clinical trials. It is proposed that the words "dissociative anesthetic" be used to describe the mental state produced by this drug.

THOSE who anesthetize[1] patients with ketamine (originally given the clinical investigation number CI-581) realize it is a unique pharmacological agent. Ever since its introduction into human clinical anesthesia, ketamine has had a turbulent history. One only has to witness ketamine anesthesia emergence delirium to realize this agent produces unique psychic effects. Nevertheless, the value and safety of ketamine in the anesthetic management of a specific subset of surgical and critical care patients is recognized. After 45 yr of ketamine use in veterinary and human clinical anesthesia, its value and side effects are well known. Why has this drug survived? What can we learn from the past? Can knowledge about ketamine guide us in the future to help in the mission of anesthesiology to relieve pain and suffering? What are its

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potential new therapeutic uses? But that is a later story… In 1823, Lord Byron wrote in canto 14 of his poem Don Juan "'Tis strange—but true; for truth is always strange; stranger than fiction."

In the Beginning

The strange story of ketamine begins with two Parke Davis (Detroit, MI) scientists. A medicinal chemist V. Harold Maddox, Ph.D., discovered a new chemical organic Grignard reaction. It led to the synthesis of phencyclidine (which was later given the clinical investigation number CI-395) on March 26, 1956.[1] Parke Davis pharmacologist Dr. Graham Chen, M.D., Ph.D. and his associates received the compound from Maddox on September 11, 1958. In animal studies, it caused an excited drunken state in rodents, but a cataleptoid immobilized state in pigeons. Their studies were extended to a large number of animals.[2] The researchers were amazed with its unusual pharmacology. Maurice H. Seevers, M.D., Ph.D. (1901–1977), Head of Pharmacology at the University of Michigan, Ann Arbor, Michigan, was contracted as their pharmacology consultant. At the time, I was a young assistant professor of pharmacology in his department. Dr. Seevers suggested I study phencyclidine further and arranged to obtain a Parke Davis grant to do so.[3] I found that the compound produced canine delirium. In monkeys, it was a remarkable anesthetic.

After sufficient animal toxicity testing, phencyclidine was given to humans undergoing surgery. John E. Gajewski, M.D., at Parke Davis was responsible for its clinical development. This was initiated at Detroit Receiving Hospital with Ferdinand E. Greifenstein, M.D. (1915–1997), Chair of Anesthesiology at Wayne State University, Detroit, Michigan, and Detroit Receiving Hospital. As in monkeys, phencyclidine was a safe anesthetic in humans. However, some patients had severe and prolonged postsurgery emergence delirium. They stated that they did not feel their limbs, as if they were sensory deprived.[4] Dr. Greifenstein contacted John Stirling Meyer, M.D., Head of Neurology at Wayne State University, to do further studies. They concluded that phencyclidine produced a "centrally mediated" sensory deprivation syndrome.[5]

At the same time, Elliott Luby, M.D. (born 1924), a psychiatrist at the Lafayette Clinic (the primary Michigan Department of Mental Health psychiatric research hospital associated with Wayne State University) was interested in sensory deprivation as a model of schizophrenia.[6] He decided to study CI-395. He and his colleagues determined the effects of phencyclidine in nine normal and nine schizophrenic patients. Phencyclidine caused the latter to become more assertive, hostile, and unmanageable. In both groups the drug state had "an impressive similarity to the schizophrenic syndrome…"[7,8] Dr. Luby learned that I had done some of the preclinical studies with phencyclidine. He suggested to Jacques S. Gottlieb, M.D. (1902–1979), the Director of the Lafayette Clinic, that they hire me as a consultant. This led me to become involved with the Lafayette Clinic, with an appointment at Wayne State University, for the next 25 yr. Dr. Gottlieb was convinced that phencyclidine was an excellent drug model of schizophrenia and strongly encouraged further research.[9] Much of the early history and research was published based on presentations at a workshop of the American College of Neuropsychopharmacology.[10] With more clinical studies, it became clear that phencyclidine was not suitable for human anesthesia. The incidence of prolonged emergence delirium was not acceptable. Cal Bratton, M.D., Ph.D., Head of Pharmaceutical Research at Parke Davis, was convinced that a short-acting derivative would be useful because its emergence delirium would be limited and, therefore, clinically acceptable just like diethyl ether anesthesia. He approved further synthesis of related compounds. Calvin Lee Stevens, Ph.D., Professor of Organic Chemistry at Wayne State University, was a chemical consultant to Parke Davis. He decided to synthesize a unique series of phencyclidine derivatives in his laboratory. He submitted his compounds for preclinical pharmacological testing to Parke Davis. Graham Chen, M.D., Ph.D., and Duncan A. McCarthy, Ph.D., screened these in animals, especially monkeys.[11] One of the agents produced excellent anesthesia and was short acting. It was selected for human trials as CI-581, and is now known as ketamine. This created patent issues which necessitated a negotiated settlement with Dr. Stevens. Its safety profile in animals led Alex Lane, M.D., Head of Clinical Pharmacology at Parke Davis, to find someone to test it in humans.

One day in early 1964, Dr. Lane called me. He asked if I was interested in doing such a clinical pharmacology study and I readily agreed. Although I spent a lot of time in clinical anesthesiology research, I am not an anesthesiologist. I contacted one of my colleagues at the University of Michigan, Guenter Corssen, M.D. (deceased 1990), a professor in anesthesiology who was interested in intravenous anesthetics. I described to him all of the pros and cons of using a phencyclidine derivative. He agreed to participate. A detailed protocol was written, reviewed, and approved by the Human Use Committee for the Parke Davis Clinical Research Unit at the Jackson Prison in the State of Michigan.

The first human was given ketamine in an intravenous subanesthetic dose on August 3, 1964. Guenter and I gradually increased the dose from no effect, to conscious but "spaced out," and finally to enough for general anesthesia. Our findings were remarkable! The overall incidence of side effects was about one out of three volunteers. Frank emergence delirium was minimal. Most of our subjects described strange experiences like a feeling of floating in outer space and having no feeling in their arms or legs. I wanted to contact Elliot Luby, as our psychiatric consul-

tant. After all, he had done the studies with phencyclidine in normal volunteers and psychiatric patients. The Parke Davis Company researchers were concerned Dr. Luby would conclude CI-581 was schizophrenomimetic, which would stop its drug development by the Parke Davis executives and lawyers. They therefore insisted that one of their own psychiatrists observe our subjects recovering from ketamine anesthesia. Their psychiatrist concluded the subjects had an emergence reaction similar to diethyl ether. In retrospect, we humans and our animals are very fortunate Parke Davis executives agreed to develop ketamine for Food and Drug Administration approval.

At the time, there was a good deal of discussion about how Guenter, another colleague, Pete Chodoff, M.D., and I should publish our data. We finally agreed to use terms such as "dreaming," *etc.*, similar to phencyclidine. However, the Parke Davis scientists did not like it. In discussing the unusual actions of ketamine with my wife, Toni, I mentioned that the subjects were "disconnected" from their environment. Toni came up with the term "dissociative anesthetic." That is what ketamine is still called today. Some of the Parke Davis scientists were concerned about referring to ketamine as a phencyclidine derivative producing "dissociative anesthesia."

Substance of Abuse

During the late 1960s and early 1970s, many drugs were used by young people as part of "make love, not war" protests against the U.S. war in Vietnam. After ketamine was approved by the Food and Drug Administration as an anesthetic, American soldiers injured during the Vietnam War were given ketamine anesthesia because of its large margin of safety. Phencyclidine,[12] and much later ketamine, became incorporated in an extensive list of drugs of abuse. The latter led to the formation of the Drug Enforcement Administration in 1973 and the drug scheduling system we have today. Phencyclidine was in Schedule I and ketamine Schedule III. Years later, ketamine was considered for Schedule II because of its increased abuse. In my ignorance I never anticipated that these agents would be abused. Phencyclidine is synthesized in illicit chemical laboratories and is of varying purity. Ketamine is widely used in veterinary medicine. Sterile ketamine vials intended for veterinary use were and still are diverted for recreational use.

In the 1970s, we decided to develop a better and more sensitive chemical assay for ketamine and its metabolites.[13] This allowed us to study its blood levels and pharmacokinetics in humans. After Dr. Corssen left the Department of Anesthesiology, Elmer K. Zsigmond, M.D., took his place. Elmer and I decided we should "tame the ketamine tiger" by reducing its emergence delirium (see fig. 1). For the next 6 yr, we studied its clinical pharmacology, pharmacokinetics, and especially combination with sedatives and tranquilizers in great detail.[14–17] Diazepam was especially helpful in reducing the emergence delirium of ketamine.[18] Now, shorter acting agents such as midazolam and propofol are far more useful.

Fig. 1. "The Ketamine Tiger." This portrait by Marisa Wood Bassett illustrates molecular models of the two enantiomers of ketamine with the more potent one in the foreground. The subject is anesthetized with ketamine acting on the brain. The ketamine tiger is coming through the central opening of the tunnel entrance, symbolizing the need to tame it.

About 1978, the prominent physician, researcher, and mystic John C. Lilly, M.D. (1915–2001), self-administered ketamine to induce an altered state of consciousness. He summarized his many unique experiences as "a peeping Tom at the keyhole of eternity." These included sensory deprivation while submerged in a water tank, communication with dolphins, and seduction by repeated ketamine use.[19] In 1978, Moore and Alltounian reported on their personal ketamine use. Marcia Moore was a celebrated yoga teacher, Howard Alltounian, M.D., a respected clinical anesthesiologist. They reportedly got high on ketamine together and after two ketamine "trips" fell in love and became engaged after 1 week.[20] They felt they were "pioneering a new path to consciousness."[21] Ms. Moore was called the priestess of the Goddess Ketamine. She took the drug daily and apparently developed tolerance. For her, ketamine was a seductress, not a goddess. Her husband warned her of its dangers. She slept only a few hours each night. She agreed that she was wrong about a lot of things and was "going to stay with it until it is tamed." However, Moore was unable to tame the ketamine tiger and in January 1979 disappeared. The assumption was that she injected herself with ketamine and froze to death in

a forest. Two years later, her skeletal remains were found.[22] Ketamine also has been used as a date rape drug. Its recreational use alone or mixed with other drugs continue to be a problem.[20,22] I am very sad and warn all that the "ketamine tiger" still ravages unsuspecting humans in the form of Bump, CatValium, K, Ket, Kit Kat, Kizzo, Special K, Super Acid, Vitamin K, Monkey Mix, or Monkey Business.

A Mechanism of Action

My early interest in phencyclidine and ketamine led to a series of collaborative studies and meetings with Asher Kalir, Ph.D. (deceased), a medical chemist in Ness-Ziona, Israel, and Jean-Marc Kamenka, Ph.D., a medical chemist in Montpellier, France.[23–25] While organizing a symposium to be held in La Grande Motte, Montpellier, France, in 1982, I was contacted by David Lodge, B.V.Sc., Ph.D., from the Royal Veterinary College in London, England. He said that ketamine caused a selective depression of cat polysynaptic reflexes *via* antagonism of N-methyl-D-aspartate (NMDA) receptors. This amazing finding caused us to invite him to present his results at that meeting. His presentation was the climax of the symposium. Now we knew the mechanism of action of ketamine as an NMDA antagonist![26,27] This led to a second United States-French Seminar held at the University of Michigan in 1987 with the potential neuroprotective effects of NMDA antagonists being especially important.[25] Four years later, another symposium in Japan provided further evidence of NMDA receptor related actions of ketamine related agents.[28] The status of ketamine in anesthesiology was the subject of a subsequent symposium in Ann Arbor.[29]

Ketamine Pharmacology

Ketamine is (S)-(+) and (R)-(−)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone and exists as two optimal isomers. It has several commercial trade names including Ketalar®, Ketaject®, Ketaset®, and Vetalar®. It is occasionally used in human anesthetic applications, especially in trauma, burn, and pediatric patients. For humans, it is available commercially, as the HCl salt, 10 and 100 mg/ml base content. It can be injected or taken orally or rectally. The drug has multiple pharmacological effects, including anesthesia, analgesia, and dysphoria, and it is sympathomimetic. Ketamine has a short blood α and β t½s of about 7 min and 2–4 h, respectively. The α t½ of ketamine in plasma is not affected by diazepam, but its peak levels are increased. The metabolites of ketamine (norketamine and nordehydroketamine) appear in venous blood about 10 and 30 min after administration. Norketamine produces similar effects as ketamine. Less is known about nordehydroketamine. Both the more potent S-(+) and the less potent R(−) enantiomers have similar pharmacokinetic profiles. In human volunteers, intravenous S-ketamine (0.15 mg/kg) is more potent than R-ketamine (0.5 mg/kg) as an analgesic.[30] The 50% equipotent doses produce equal degrees of insobriety and dizziness. However, S-ketamine produces 1.6 times greater altered body image and changes in hearing, 2.5 times greater feelings of unreality, and 4 times more reduced visual acuity. The reduction of pain score was also greater (70 *vs.* 50) for the S-isomer, suggesting a 40% possible error in analgesia scores based on single equieffective doses based on dose-effect scores. An important use of racemic ketamine nowadays is in the treatment of acute pain, especially in patients on chronic opiate therapy. Studies with the two separate enantiomers in combination with opioids would be of interest because in equianalgesic doses the more potent S-isomer appears to have greater unwanted psychic side effects than the R-isomer. Ketamine N-demethylation occurs primarily *via* CYP3A4 and less *via* CY2B6 and CYP2C9 cytochromes. Hence, concurrent drug inducers and inhibitors will reduce or enhance its blood levels. Three days after a single dose of ketamine, it is eliminated in the urine as 2.3% unchanged, 1.6% as norketamine, 16.2% as dehydronorketamine, and 80% as the conjugated hydroxylated derivatives of ketamine. Peak anesthetic induction blood levels of ketamine are as high as 9,000–25,000 ng/ml. The levels to produce or maintain anesthesia are 2,000–3,000 ng/ml. Patients awaken after plasma levels are reduced to 500–1,000 ng/ml. Concentrations of 50–100 ng/ml produce the dissociated psychic states drug abusers achieve. The psychic effects of small doses of (S)-(+)-ketamine produce related plasma levels and brain concentrations as measured by positron emission tomography in healthy volunteers.[31] From a scientific point of view, the issue of whether ketamine or its active metabolite exist in the human brain 24 h after ketamine is administered in low doses is of importance. Chronic pain patients have reported some relief lasting even longer, which is itself a topic of further research. In addition, some subjects experience dreams 24 h later. Hence, there is a need for more sleep studies. Some recreational ketamine users report marked dissociative effects for days after drug use. Schizotypical and impaired semantic memory symptoms have been described. Why is this so if the drug is no longer present in the brain? These may be important clues to its delayed beneficial and untoward side effects. This may be due to synaptic plasticity; there is a change in the brain α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate/NMDA receptor ratio.

In 1982–1984, we described a three compartment model with pharmacokinetic parameters for ketamine in adults which can be used to maintain a stable plasma concentration.[15] Subsequently, we studied the pharmacokinetics of ketamine in children using jet injection methodology.[32] Based on various studies in the literature, intravenous induction bolus doses of ketamine produce peak concentrations of 9,000–25,000 ng/ml with awakening about 1,000 ng/ml. Psychologic effects are dose-dependent. The dose of ketamine HCl usually used in psychiatric research studies is 0.5 mg/kg, given over 40 min. A 70 kg person has a ketamine

volume of distribution at steady state of about 3.1 l/kg or 217 l.[33] Hence, 35 mg in a volume of 217 l is 35 gm/217×10^3. This is 161 ng/ml, assuming no metabolism or excretion. Although this is a blood level that does not produce major side effects, it does produce psychiatric changes.

In anesthetic concentrations, ketamine has several mechanisms of action besides antagonism of excitatory amino acids on NMDA receptors. S(+)-ketamine is 2–3 times more potent than R(−)-ketamine at μ, κ, and δ opioid receptors.[34] Racemic ketamine displaces [^{125}I] Tyr 14 nociceptin with 0.5 mM. Racemic ketamine inhibits naloxone insensitive cyclic adenosine monophosphate. A 50% inhibition is produced by 2 mM. Ketamine in 100 μM reverses [D-Ala2,N-MePhe4,Gly-ol]enkephalin (μ) and spiradoline (κ) inhibition of cyclic adenosine monophosphate. Ketamine potentiates the antinociceptive effects of μ, but not κ or δ agonists in a mouse acute pain model.[35] Ketamine also inhibits α6 nicotinic acetylcholine receptors. Some actions of ketamine that are important issues need further research. For example, ketamine blocks myocardial adenosine trisphosphate-sensitive potassium channels in rat ventricular myocytes. The latter effect suggests ketamine may reduce the cardioprotective effects of adenosine trisphosphate-sensitive potassium channels during ischemia and reperfusion.[36]

Phencyclidine, ketamine, dizocilpine (MK-801), dextromethorphan, and memantine are all noncompetitive NMDA antagonists that bind within the channel. As use and voltage-dependent inhibitors they require the ion channels to open to allow access. Upon channel blockade, slow dissociating compounds with high affinity like MK-801 are trapped within the channel. Low affinity channel blockers which dissociate faster, such as ketamine and especially memantine, provide a better therapeutic index than high affinity blockers. These agonists, including the anesthetic gas nitrous oxide, consistently produce vacuoles in the retrosplenial cortex of animals and have been interpreted as neuropathologic changes.[37–41] This includes memantine approved by the Food and Drug Administration as adjunctive therapy of Alzheimer's disease. It is unknown whether these agents produce similar changes in primates. The retrosplenial cortex is involved with episodic memory, special navigation, imagination, and future planning. Patients with mild cognitive deficit and early Alzheimer's disease have decreased ^{18}F-deoxyglucose metabolism in this brain region.[42]

Ketamine and Pain Mechanisms

The acute analgesic effects of ketamine in human volunteers were reported many years ago.[43,44] In 1987 Davies and Lodge found that NMDA receptors were involved in frequency dependent potentiation of the response (wind-up) of class 2 neurons in rat dorsal horn. Iontophoretic kynurenate, an allosteric modulator of the NMDA receptor, reduced both the initial response and the wind-up.[45] On the other hand, iontophoretic or intravenous ketamine had no consistent effect on the initial response, but always reduced wind-up. They concluded NMDA receptors were involved with the wind-up response to repeated noxious stimulation. Since 1994, a great deal of clinical research has demonstrated that ketamine is a very effective analgesic in chronic pain syndromes that involve a wind-up mechanism. These include postherpetic neuralgia, migraine, burns, neuropathies, and fibromyalgia. One of the current uses of ketamine in low doses is also to enhance the analgesic effect of opioids. The current extensive literature on the analgesic actions of ketamine deserves a separate review.

Ketamine Antidepressant Effects

Truth is indeed stranger than fiction! Many years ago when I was a clinical pharmacologist working part time at the Lafayette Clinic, I ran the drug abuse screening laboratory. I was often referred drug abuse patients by the attending psychiatrists. Several referrals dealt with phencyclidine and ketamine drug abuse, especially in the late '70s and early '80s. A number of these patients were mentally depressed, taking various antidepressants off and on. I remember one young lady, in particular, who was a chronic phencyclidine and later ketamine abuser. She had serious bouts of mental depression. I asked her why she took these illicit drugs rather than her usual antidepressant medications. Her answer was "Oh, doctor, my antidepressants don't work as well." She stated that ketamine and phencyclidine worked quickly and were much better antidepressants but they didn't last as long so she took them again and again. I promptly recommended that she stop this bizarre practice because it would only harm her. I never pursued the possible antidepressant actions of ketamine. After all - I knew better! In low doses, phencyclidine and ketamine were schizophrenomimetic. Javitt and Zukin reviewed the more recent advances in the phencyclidine model of schizophrenia which further reinforced my previous rigid beliefs.[46]

Starting about 16 yr ago, John Krystal, M.D., and his colleagues used very low dose ketamine intravenous infusion in a series of important studies.[47–51] Both normal subjects and psychiatric patients were studied, again with the idea that low dose ketamine was a good model of schizophrenia. The unexpected finding was that ketamine also had antidepressant effects in depressed patients.[52] Kudoh *et al.*[53] reported it to be antidepressant in surgical patients during their postoperative period. In addition Correll and Futter reported two cases of subanesthetic doses of ketamine in major depressive disorder.[54] What

was the truth with these strange reports? Were they fact or fiction? When Zarate *et al.*[55] reported their positive results with ketamine in a randomized trial of treatment-resistant major depression, I became a believer. I thought of my Lafayette Clinic referral patient of years ago. Again I learned an important lesson. Doctor, listen to your patients and what they tell you! The next year another case report of the antidepressant effects of ketamine appeared.[56] Goforth and Holsinger also reported rapid relief of severe depression by preoperative ketamine and electroconvulsive therapy.[57] Weg received a U.S. patent for the nasal administration of ketamine.[58] Charney *et al.*[59] subsequently applied for a U.S. patent on intranasal ketamine to treat depression. Valentine *et al.* also reported beneficial antidepressant effects in a group cross-over single blind study of low dose (0.5 mg/kg intravenous over 40 min) ketamine in 10 depressed patients.[60] Aan het Rot *et al.*[61] reviewed the published clinical evidence to date of the antidepressant effects of ketamine, pros, cons, and areas of uncertainty regarding the future use of racemic ketamine and its enantiomers. Surely, the study of the basic mechanisms of ketamine's antidepressant effects will provide new lead targets to develop better agents to treat therapy resistant patients.

Conclusion

Where do we all go from here? The 50th anniversary of the introduction of ketamine in humans will be in 2014. Perhaps by then we will have a better understanding of the place of this unusual agent that exists as right and left handed enantiomers. One is less potent than the other, but are they equally effective? And effective for what – anesthesia, analgesia, or mental depression? We need more research! In the meantime you, the reader, must decide what is truth or fiction in your clinical use of ketamine or its separate enantiomers. But always be aware of that tiger…it needs to be tamed.

References

1. Maddox VH, Godefroi EF, Parcell RF: The synthesis of phencyclidine and other 1-arylcyclohexylamines. J Med Chem 1965; 8:230–5
2. Chen G, Ensor CR, Russell D, Bohner B: The pharmacology of 1-(1-phenylcyclohexyl) piperidine HCl. J Pharmacol Exp Ther 1959; 127:241–50
3. Domino EF: Neurobiology of phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. Int Rev Neurobiol 1964; 6:303–47
4. Greifenstein FE, Devault M, Yoshitake J, Gajewski JE: A study of a 1-aryl cyclohexylamine for anesthesia. Anesth Analg 1958; 37:283–94
5. Meyer JS, Greifenstein F, Devault M: A new drug causing symptoms of sensory deprivation. J Nerv Ment Dis 1959; 129:54–61
6. Cohen BD, Rosenbaum G, Dobie SI, Gottlieb JS: Sensory isolation: Hallucinogenic effects of a brief procedure. J Nerv Ment Dis 1959; 129:486–91
7. Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R: Study of a new schizophrenic drug, Sernyl Arch Neurol Psychiatry 1959; 81:363–9
8. Rosenbaum G, Cohen BD, Luby ED, Gottlieb JS, Yelen D: Comparison of Sernyl with other drugs: Simulation of schizophrenic performance with Sernyl, LSD-25, and amobarbital (Amytal) sodium I Attention, motor function, and proprioception Arch Gen Psychiat 1959; 1:651–6
9. Luby ED, Gottlieb JS, Cohen BD, Rosenbaum G, Domino EF: Model psychoses and schizophrenia. Am J Psychiat 1962; 119:61–7
10. Domino EF, ed.: Phencyclidine: Historical and Current Perspectives. Ann Arbor, NPP Books, 1981, pp. 1–537
11. McCarthy DA, Chen G, Kaump DH, Ensor C: General anesthetic and other pharmacologic properties of 2(o-chlorophenyl)-2-methylaminocyclohexanone HCl (CI-581). J New Drugs 1965; 5:21–33
12. Domino EF: From Sernyl to angel dust: The return of PCP. University of Michigan Medical Center Journal XLVII 1981b; 1–5
13. Lau SS, Domino EF: Gas chromatography mass spectrometry assay for ketamine and its metabolites in plasma. Biol Mass Spectrom 1977; 4:317–21
14. Domino EF, Zsigmond EK, Domino LE, Domino KE, Kothary SP, Domino SE: Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. Anesth Analg 1982; 61:87–92
15. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK: Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clin Pharmacol Ther 1984; 36:645–53
16. Zsigmond EK, Domino EF: Ketamine-clinical pharmacology, pharmacokinetics and current clinical uses. Anesthesiol Rev 1980a; 7:13–33
17. Zsigmond EK, Domino EF: Clinical pharmacology and current uses of ketamine. In: Aldrete JA, Stanley TH (Eds.). Trends in Intravenous Anesthesia. Miami, Symposia Specialists, 1980, pp. 283–330
18. Fontenot J, Wilson RD, Domino EF, Zsigmond EK, Steen SN, Aldrete JA, McDonald JS, Fox GS: Efficacy and safety of low-dose intravenous (mini-drip) ketamine hydrochloride and concurrent intravenous diazepam in the induction and maintenance of balanced anesthesia. Clin Pharm Ther 1982; 31:225–6
19. Lilly JC: The Scientist: A Metaphysical Autobiography, 3rd Edition. Oakland, CA: Ronin Publishing, 1997, pp. 1–232
20. Jansen KL: Ketamine: Dreams and Realities. Multidisciplinary Association for Psychedelic Studies (MAPS). Sarasota, FL 2001, pp. 50–55
21. Moore M, Alltounian H: Journeys into the Bright World. Rockport, Para Research, 1978, pp 1–184
22. Jansen KL: A review of the nonmedical use of ketamine: Use, users and consequences. J Psychoactive Drugs 2000; 32:419–33
23. Kamenka JM, Domino EF: Phencyclidine and related arylcyclohexylamines. Ann Arbor, NPP Books, 1983
24. Kamenka JM, Domino EF: Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection. Ann Arbor, NPP Books, 1992
25. Domino EF, Kamenka JM: Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology. Ann Arbor, NPP Books, 1988
26. Lodge D, Ands NA, Berry SC, Burton NR: Arylcyclohexylamines selectively reduce excitation of mammalian neuroncs by aspartate-like amino acids. In: Phencyclidine and Related Arylcyclohcxylamincs (Kamenka JM, Domino EF, Geneste P, eds). Ann Arbor, NPP Books, 1983, pp 595–616
27. Anis NA, Berry SC, Burton NR, Lodge D: The dissociative

anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by N-methyl-aspartate. Br J Pharmacol 1983; 79:565–75

28. Kameyama T, Nabeshima T, Domino EF, eds.: NMDA Receptor Related Agents: Biochemistry, Pharmacology, and Behavior. Ann Arbor, NPP Books, 1991, pp 1–414
29. Domino EF, ed.: Status of Ketamine in Anesthesiology. NPP Books, Ann Arbor, 1990, pp 1–583
30. Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 1992; 260:1209–13
31. Hartvig P, Valtysson J, Lindner KJ, Kristensen J, Karlsten R, Gustafsson LL, Persson J, Svensson JO, Oye I, Antoni G, Westerberg G, Langstrom B: Central nervous system effects of subdissociative doses of (S)-ketamine are related to plasma and brain concentrations measured with positron emission tomography in healthy volunteers. Clin Pharmacol Ther 1995; 58:165–73
32. Domino EF, Zsigmond EK, Kovacs V, Fekete G, Stetson P: A new route, jet injection for anesthetic induction in children—III. Ketamine pharmacokinetic studies. Int J Clin Pharmacol Ther 1997; 35:527–30
33. Evers AS, Crowder CM, Balser JR: General anesthetics. Chapter 13, in Goodman and Gilman's The Pharmacological Basis of Therapeutics 11 Ed., eds. LL Brunton, JS Lazo, KL Parker, McGraw Hill, 2006, pp 341–68
34. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG: Stereoselective interaction of ketamine with recombinant μ, κ, and δ opioid receptors expressed in Chinese hamster ovary cells. ANESTHESIOLOGY 1999; 90: 174–82
35. Baker AK, Hoffman VL, Meert TF: Dextromethorphan and ketamine potentiate the antinociceptive effects of mu- but not delta- or kappa-opioid agonists in a mouse model of acute pain. Pharmacol Biochem Behav 2002; 74:73–86
36. Ko SH, Lee SK, Han YJ, Choe H, Kwak YG, Chae SW, Cho KP, Song HS: Blockade of myocardial ATP-sensitive potassium channels by ketamine. ANESTHESIOLOGY 1997; 87:68–74
37. Olney JW, Labruyere J, Price MT: Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 1989; 244:1360–2
38. Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA: NMDA antagonist neurotoxicity: Mechanism and prevention. Science 1991; 254:1515–8
39. Jevtovic-Todorovic V, Todorovic SM, Mennerick S: Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 1998; 4:460–3
40. Jevtovic-Todorovic V, Benshoff N, Olney JW: Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. Br J Pharmacol 2000; 130:1692–8
41. Jevtovic-Todorovic V, Carter LB: The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain. Neurobiol Aging 2005; 26:947–56
42. Vann SD, Aggleton JP, Maguire EA: What does the retrosplenial cortex do? Nature 2009; 10:792–803
43. Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 1965; 6:279–91
44. Corssen G, Domino EF: Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative Cl-581. Anesth Analg 1966; 45:29–40
45. Davies SN, Lodge D: Evidence for involvement of *N*-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Res 1987; 242:402–6
46. Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiat 1991; 148:1301–8
47. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses Arch Gen Psychiat 1994; 51:199–214
48. Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrissey K, Abi-Saab D, Bremner JD, Bowers MB Jr, Suckow RF, Stetson P, Heninger GR, Charney DS: Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacol 1998; 135: 213–29
49. Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S, Stetson P, Trevisan LA, Charney DS: Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiat 1998; 55:354–60
50. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB Jr, Vegso S, Heninger GR, Charney DS: Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology 1999; 145:193–204
51. Krystal JH, Bennet A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS: Dissociation of ketamine effects on rule acquisition and rule implementation: Possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiat 2000; 47:137–43
52. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH: Antidepressant effects of ketamine in depressed patients. Biol Psychiat 2000; 47:351–4
53. Kudoh A, Katagai H, Takazawa T: Antidepressant treatment for chronic depressed patients should not be discontinued prior to anesthesia. Can J Anaesth 2002; 49:132–6
54. Correll GE, Futter GE: Two case studies of patients with major depressive disorder given low dose (subanesthetic) ketamine infusions. Pain Med 2006; 7:92–5
55. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK: A randomized trial of an N-methyl-Daspartate antagonist in treatment-resistant depression. Arch Gen Psychiat 2006; 63:856–64
56. Liebrenz M, Borgeat A, Leisinger R, Stobler R: Intravenous ketamine therapy in a patient with a treatment-resistant major depression. Swiss Med Weekly 2007; 137:234–6
57. Goforth HW, Holsinger T: Rapid relief of severe major depressive disorder by use of preoperative ketamine and electroconvulsive therapy. J ECT 2007; 23:23–5
58. Weg SL: Nasal administration of ketamine to manage pain. US Patent 5,543,434, August 6, 1996
59. Charney DS, Mathew SJ, Manji HK, Zarate CA, Krystal JH: Intranasal Administration of Ketamine to Treat Depression. US Patent Application 20070287753. December 13, 2007
60. Valentine G: The acute effects of ketamine on mood and occipital cortex amino acid neurotransmitter content. Biol Psychiat 2007; 61(suppl 1):233
61. Aan het Rot M, Charney DS, Mathew SJ: Intravenous ketamine for treatment-resistant major depressive disorder. Prim Psychiat 2008; 15:39–47