A Review of the Nonmedical Use of Ketamine: Use, Users and Consequences

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Abstract—Ketamine is a dissociative anesthetic with an accepted place in human medicine. Ketamine also has psychedelic properties, and there has been a recent increase in nonmedical use linked with the growth of the "dance culture." This has attracted little comment in the formal literature but has been the subject of many reports in the media. Myths and misunderstandings are common. The psychedelic properties of ketamine have also led to its use as an adjunct to psychotherapy. This review is intended as a resource for the wide range of persons now requesting accurate information about the nonmedical use of ketamine. It accepts the current necessity of sometimes referring to anecdotal reports while seeking to encourage an increase in formal research. The review includes the history of ketamine, its growing role as a "dance drug," the sought-after effects (including the near-death experience) for which it is taken in a nonmedical context, how these are produced, common mental and physical adverse effects, and the ketamine model of schizophrenia.

Keywords—ketamine, NMDA (N-methyl-D-aspartate) receptors, near-death experience (NDE), phencyclidine (PCP), psychedelic, schizophrenia

> I can't understand why anybody would want to take the stuff. It gives you nightmares, doesn't it?
>
> Consultant psychiatrist in addictions, 1996

> That 22 minute journey to becoming the intelligence at the heart of the universe remains the most powerful and cosmic experience of my life.
>
> Ketamine user, 1997

In 1962, Calvin Stevens invented ketamine at the Parke-Davis laboratories in Michigan. The new drug was related to PCP (phencyclidine) but was shorter acting and far less toxic, producing a trance-like "dissociative anaesthesia" (Domino, Chodoff & Corssen 1965). Ketamine was soon launched into the psychedelic underground, sold as "rockmesc" along the Florida coast, and noted in underground literature (e.g., Shelton & Sheridan 1975). In 1970, the FDA approved ketamine for human use and it became popular as a battlefield anesthetic. It was (and still is) legally sold as Ketalar® (Parke-Davis, for humans), Ketaset® (Fort Dodge, for animals), and other brands. Warnings about the drug's potential for unauthorized use soon appeared in the medical literature (Reier 1971) as ketamine appeared more widely on the unauthorized drug market, with street use of solutions first officially noted in California in 1971 (Siegel 1978). Young and colleagues (1977) believed that recreational use of ketamine might be partly attributed to experiences gained in Vietnam, where it was used as an anaesthetic.

By the end of the decade, the FDA was concerned about nonmedical use (FDA 1979), especially after publication of accounts such as *Journeys into the Bright World* (Moore & Alltounian 1978) and *The Scientist: A Novel Autobiography* (Lilly 1978), the report by Siegel (1978) and discussions in *Psychedelic Drugs Reconsidered* (Grinspoon & Bakalar 1979), *Psychedelics Encyclopaedia* (Stafford 1992, originally published in 1978), and *High Times* (Ashley 1978).

Marcia Moore was a famous author of New Age books. She first took ketamine in 1976 (at age 48) with friends in California. A year later she suggested taking ketamine to

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Howard Alltounian, M.D., an anesthetist who came to one of her workshops. After two such "journeys" together, as they called them, they became engaged, having known each other for just a week:

> The spell was raying forth in a multihued canticle, a garland of love woven with bands of light . . . the next ten minutes or so were the most emotionally intense . . . the Goddess Ketamine had put the seal of approval on our union . . . At the point of emergence I often did weep and my tears seemed to be drops drawn directly from a shoreless sea of inexpressibly deep feeling . . . ketamine works primarily on the "emotional body" whereas LSD is more mental in its effects . . . (Moore & Alltounian 1978).

Moore named what she perceived to be the highest level of her experiences "the cosmic matrix" or "cosmatrix"—the source from which everything was said to be derived. She noted that ketamine produced a "higher, clearer and more real trip" than LSD, although some people just felt "disconcertingly whacked out," and that ketamine produced fragmentation into subpersonalities, including her role as "priestess of the Goddess Ketamine." She took the drug with ever-increasing frequency and noted a rapid tolerance; her mental boundaries became more porous as "the message of the Goddess" was interpreted as "let the soul (the light) seep through," and there was an apparent increase in magical coincidences between mental and physical events. By early 1978, she was taking the drug daily and only slept for three hours per night. She went to visit John Lilly, who had just been through a prolonged ketamine binge and near-fatal accident. She told him that she intended "to ride this comet through to the end":

> John Lilly's last words to me were: "you'd better be damn strong if you're going to play that game". . . As this book goes to press I have once again increased the doses. (Moore & Alltounian 1978).

"The Priestess," aged 50, disappeared on a freezing winter's night in January of 1979. Her bleached skeleton was found two years later. She had gone at night into a nearby forest, and frozen to death after injecting herself with all the ketamine she could find (Jansen In press).

> Marcia became addicted to ketamine. . . . The drug is dangerous and its use should not be encouraged. . . . I told her that it was a Seductress, not a Goddess. (Howard Alltounian, interviewed in Jansen In press).

Psychonaut John Lilly, M.D., spent decades exploring his own mind using flotation tanks, ketamine and other drugs (Lilly 1978). His first ketamine binge lasted for a year. After his wife found him floating face down in the pool and had him rushed to hospital, she tried to persuade him to seek help, telling him that ketamine had taken over his life, but he felt that there were further parameters to be explored, and spent a month injecting himself almost hourly. He became convinced that he had to warn the government about an extraterrestrial plot; he collapsed in a toilet and was taken to hospital again but soon returned home to continue "exploring the parameters." Lilly became convinced that he was a time traveler from the future, that he was controlled by a "solid-state entity," and that there were messages for him on television. Word spread that he had a serious problem, his sources dried up, and there followed a period of severe psychological withdrawal (Lilly 1978). There were further accidents and alarming events, but Lilly survived and was still using ketamine at the age of 83.

The ketamine experiences Lilly described were based around contact with "other beings" and they had an inhuman, cold and computer-like flavor, infused with the chill of space, in contrast to the earthy warmth and emotion of Moore's adventures with the "Goddess Ketamine." Lilly was himself sometimes seen as rather distant at this time, while Moore was concerned with love, emotion and the Earth. *Journeys into the Bright World* vanished but *The Scientist* was still available, feeding a popular perception that ketamine is cold and inhuman. It is an error to ascribe coldness or warmth to molecules, as these are attributes of their users. Nevertheless, there is some objective support for Lilly's view that ketamine can sometimes produce an emotion-free state of what he called "high indifference." Brain scans show that at psychedelic, subanaesthetic doses, the higher brain (neocortex) is very "on" while parts of the older, more emotional brain may be "off" until the ketamine levels fall (Vollenweider et al. 1997 a, b). This fits Moore's observation that the "higher realms were pure mentation" and it was not until she had "descended" that emotions returned (Moore & Alltounian 1978).

KETAMINE AND THE DANCE CULTURE

Until the mid-1980s, nonmedical use of ketamine was often identified with mind explorers and alternative (New Age) spirituality, and was linked to those with access to the drug, such as medical and bioscience professionals (Weil & Rosen 1983). Most case studies of ketamine dependence are still drawn from this pool of home-setting self-injectors (Moore & Bostwick 1999; Hurt & Ritchie 1994; Soyka, Krupitski & Volki 1993; Jansen 1990b; Kamaya & Krishna 1987; Ahmed & Petchkovsky 1980). However, since the mid-1980s there has been increased ketamine use linked with the growth of the "dance culture" of techno clubs, parties and raves (Curran & Morgan 2000; Weiner et al. 2000; Skovmand 1996; Dotson, Ackerman & West 1995; Jansen 1993). Ketamine is a stimulant at low doses (White & Ryan 1996) and some users can still dance while affected by it, especially when the drug is combined with other stimulants that reduce dissociation. The dance culture began in American night clubs around 1980 and spread to the beach parties of Goa (India) and Ibiza (Spain). European DJ's returned home

with new drugs such as ecstasy (MDMA, methylenedioxymethamphetamine) and ketamine (bought over the counter in Goa) to stage free parties in warehouses, barns and fields. By 1993, the dance culture had became so large that it reduced profits in the liquor industry, as ravers drank water and avoided alcohol. Alarmed lobbyists, amongst others, encouraged the U.K. government to write a section into the Criminal Justice and Public Order Act of 1994 outlawing unlicensed parties where techno music was played. The Act required that parties be licensed, forcing them into venues where alcohol was sold. By banning the free parties from barns and paddocks, the law helped to push the use of all the "dance drugs" into the mainstream of society, as the approved venues were also used by mainstream people. With the profits of all sides assured, the dance culture grew even faster and was then re-exported to many other countries (e.g., Topp et al. 1998).

The figures for nonmedical ketamine use are largely unknown as it has yet to be included in statistically valid surveys, but rising use has been noted in both fashion and dance magazines (e.g., Crysell 1998; Jansen 1997c) and the mainstream media, which reacted with articles such as "Party Craze for Cat's Drug" (Reuter 1996), "Is Your Kid on K?" (Cloud 1997), "Drug Users Adopt Bad Trip Anaesthetic" (Hall & Cassidy 1992) and "Sedate Rape" (Cosmopolitan 1997). A survey was conducted in 1996, involving interviews at 18 venues throughout the southeast of England. Respondents were selected on an anonymous, randomized basis. Of the 496 participants (70% aged between 19 and 24), 31% had used ketamine and 85% had used ecstasy (Release 1997). Ketamine-induced disorders were included for the first time in books such the *Handbook of Psychiatric Emergencies* (Slaby 1994), and 1994 was also the year that the *Australian Illicit Drug Report* included ketamine for the first time (Australian Bureau of Criminal Intelligence 1995). The U.S. Drug Enforcement Agency website and related sources warned that ketamine abuse was rising (Anonymous 1997; DEA 1997; Brown 1995). Ketamine was featured in an *X-Files* episode in 1997, where it was used to recover lost memories, and was mentioned in the film *Armageddon* in 1998. It was not mentioned in the film *Altered States*, a popular myth, and did not inspire the record "K" by Kula Shaker, although the drug has had an effect on music (e.g., the Chemical Brothers' "Lost in the K-hole," Mrs. Wood's "K-Street Detour," the Higher Intelligence Agency's "Ketamine Entity," and music by the techno DJ Danny Tenaglia).

In the U.K., many (but certainly not all) party/clubgoers first took ketamine accidentally in a pill that was sold to them as ecstasy. The results of this surprise attack were often unpleasant, and ketamine acquired a bad reputation. When swallowed, the drug is absorbed into blood which goes to the liver first, where most of it is changed into norketamine before reaching the brain (Grant, Nimmo & Clements 1981). Norketamine has more numbing and sedating effects and lasts longer than ketamine (Humphries, Melson & Gore 1997). Ketamine was also taken in its own right by a faction of the "free party/crusty/ traveller" (U.K.) subculture from the outset, because ketamine imports from India were then cheap while ecstasy was expensive. Some of those who took ketamine with alcohol would then physically bump into others and behave without regard for the social mores, increasing ketamine's bad reputation. In contrast, in the United States and Australia ketamine has usually been a relatively expensive drug taken by affluent students and professionals (Jansen In press; Topp et al. 1998). The European situation changed as more users took ketamine by the intranasal route, increasing its popularity (Dalgarno & Shewan 1996).

Medical staff have now injected ketamine into millions of people for anaesthetic and analgesic purposes, mostly in developing countries as an anesthetist is not essential (Ketcham 1990), although Parke-Davis (2000) now states that ketamine should only be given by a specialist in a hospital, with resuscitation equipment at hand. In developed countries, ketamine is still widely used as an anaesthetic (e.g., Green et al. 1998) but is increasingly controversial (Sobel, Morgan & Murphy 1999). The usual media description of it as a horse, cat or elephant tranquilizer is thus misleading; ketamine still has an accepted place in modern human medicine. In August 1999, ketamine became a Schedule III drug at the federal level in the United States, and controls are increasing elsewhere. For example, in 1999 in the state of Victoria, Australia, ketamine was listed in Schedule II as a drug of dependence requiring a stricter enforcement regime, and specific penalties were introduced for using, possessing and trafficking in ketamine (Australian Bureau of Criminal Intelligence 2000). In Europe, ketamine could still be ordered legally from chemical companies in October 2000. It was also stolen from animal hospitals, laboratories and hospitals, and smuggled from other countries. In the U.K., ketamine is not controlled by the Misuse of Drugs Act, but sale is restricted by the Medicines Act. In practice, the U.K. police ignore ketamine and prosecutions are rare, except when it is sold as fake ecstasy pills and prosecuted as conspiracy to offer to supply a class A drug (MDMA) . This may have led to a false impression among those who rely on arrest and conviction reports as to the real extent of nonmedical ketamine use.

All brands are not identical. Ketalar® contains a preservative (benzthonium chloride) which may have mental effects (Durieux & Nietgen 1997). Other brands (e.g., German brandAstrapin®) contain chlorobutanol, which is toxic in some animal models (Borgbjerg et al. 1994; Malinovsky et al. 1993). One brand contains only S(+)ketamine rather than the equal mixtures of S(+) and R(-)ketamine (different molecular shapes) found in Ketalar® and Ketaset®. S(+)ketamine causes faster loss of consciousness, is more likely to suppress breathing, and has a faster recovery time (Engelhardt 1997). S(+)ketamine is a more potent

psychedelic drug than R(-)ketamine; the rumor that "it's a new ketamine without the psychedelic part" is incorrect (Vollenweider et al. 1997a).

THE DOORS OF DISSOCIATION

Ketamine is a psychedelic ("mind revealing") drug because it can sometimes reveal aspects of how the mind constructs reality, personality, and a sense of meaning and sacredness, without necessarily inducing a toxic delirium. The term "hallucinogen" is inadequate for describing increased empathy, insights, reliving old memories, religious ecstasy and many other effects (Grinspoon & Bakalar 1979), while the term "entheogen" refers only to spiritual aspects. Timothy Leary observed that ketamine and Salvinorin A were the most profound psychedelic drugs in terms of the perceived depths of the experience (Leary & Sirius 1997) and *The Essential Guide to Psychedelics* described ketamine as the "ultimate psychedelic journey" (Turner 1994). The experience is affected by the dose, route, set (personality, history, mood, motivations, intelligence, imagination, attitudes, life events and expectations of the user) and setting (the physical, social and emotional environment; e.g., Kumar et al. 1992). Sklar and colleagues (1981) concluded that a warm, understanding doctor who stressed positive aspects and told patients to think of a pleasant image produced the best reports post-anesthesia.

Effects begin about 30 seconds after an intravenous (i.v.) injection, two to four minutes after an intramuscular (i.m.) injection, five to 10 minutes after intranasal use, and 10 to 30 minutes after an oral dose on an empty stomach or by rectal injection (using a lubricated syringe with the needle removed—ketamine has an unpleasant taste and irritates the nose). The duration of the psychedelic effects varies from 10 minutes (i.v.) to an hour (i.m.) to four hours (oral). Psychedelic doses are about 10% to 25% of anesthetic doses, by the same route; 100mg taken i.m. will produce an hour-long experience, with full normality returning within three hours. The effects can have a much shorter duration in persons with a tolerance. A club "bump" for intranasal use is 200mg; psychedelic doses for i.m. use are 50-150 mg, while oral doses are usually 350-500mg. Intranasal use can produce anesthetic blood levels (Malinovsky et al. 1996), and some users take up to a gram by this route:

> I used pure K in the NY Club scene (nasally) . . . "beyond words" experiences, deep thoughts of family, in touch with GOD, another dimension of "reality" . . . experimenting with K has changed my whole outlook on life, "death?", and GOD. I miss the deepness and extreme spirituality of the experience. At times during the trip, I reflected on my entire life, remarkably lucid visions of my birth . . . (interview in Jansen In press).

The effects may include a sense of merging with another person or group, and a sense of becoming an animal, plant, or inanimate matter. Awareness may seem to expand to include the entire universe. There may be apparent: out-of-body experiences; transcendence of time including foetal, ancestral, racial and past life trips; experiences of evolution and appearing to see events in the future or the past; apparent extension of awareness beyond consensus reality and space-time into other universes, symbols, the dead, energy fields, archetypes and a merging with the Ultimate Reality from which the "illusions" of time, space and matter appear to be derived; and a link between the mind and physical events in ordinary reality (e.g., synchronicity). The sense of time can vanish completely. Plants have been used for magical purposes in pre-industrial societies; ketamine is a modern drug, and has been used in this way by "modern magicians":

> I settled on a form which involved banishing, consecrating and performing a full invocation. I would then take a dose of K and don a pair of headphones which would play me a pre-recorded hypnotic instruction beginning with basic trance induction. . . . No longer was I in my New York apartment; I was in Egypt, inside a pyramid. I was lying inside an open sarcophagus. The inside of the chamber was brightly lit, a bluish-white light adhering to everything and also radiating very strongly from me. I felt that this light, which moved through me, and radiated from me, connected me with . . . everything else through space and time, especially a moment in space-time when a man in New York was lying within a magic circle in the 20th century . . . (Farber 1995)

Some ketamine experiences resemble lucid dreaming in which people are aware that they are dreaming, and can influence and control the dream. At higher doses, the drug is sometimes perceived as having its own agenda. Other experiences are like virtual reality games or a journey through information networks. A "brick of ketamine" was mentioned in William Gibson's 1984 book *Neuromancer*, which is about launching awareness itself into a form of the World Wide Web. Some parts of films such as *Tron* and *The Matrix* (in which the central character is given a choice of two pills, representing dream and reality, in an echo of Alice in Wonderland) give an impression of some of these features. Some other reasons why ketamine is taken in a nonmedical context include recovery of forgotten memories (see A below), problem solving (B), bonding and love (C) and for spiritual experiences (D). All quotes are abridged from accounts discussed in Jansen (In press):

A: I was able to discover the hidden meanings behind every door that was normally closed. . . . I also remembered events as a child...things I would never normally remember. I never felt as if I was not myself, my memory and intelligence seemed dramatically enhanced. . . . There was no feeling of depression afterwards, only calmness and inner peace. . . .

B: I would take doses in a plastic minibag with me to parties

and a straw which I inserted into the bag to dose myself. . . . I would pace doses at least an hour apart by affixing an hour-burning incense stick to the back of my wheelchair . . . it certainly helped to be sitting down, surrounded by mad dancers and throbbing music. I would have many great revelations on the dance floor that would often relate to either a graphic design project, or a book I was writing, and I took to carrying a micro-cassette recorder to record these ideas for later development—with great success. . . .

C: Low dose K was pure emotion, no thinking. Just a warm, golden sun of love for my partner into which I could dive like a pool. If you take K in the dark by yourself, it'll be cold. If you take 50mg i.m. in a warm sunny bedroom with a friend you'll have a very different experience. Where you are and who you are with do count for K. . . . People who think they're made of plastic and have turned into computers are telling us something about themselves as well as something about the drug. . . .

D: I was actually God. I distinctly felt the universe watching for my signal to see if it should cycle through itself once again, as it had an infinite number of times, or should it simply conclude. It felt so beyond unquestionably real, it was just as plain and crisp as it could be, not some hallucination. . . .

Changes in the perception of body parts are common (Hansen et al. 1988), music may not be heard at all or it can seem very loud with selection of particular frequencies (Plourde, Baribeau & Bonhomme 1997), and there can be colorful visions, particularly of being in a vast space or building. New words are formed with meanings that cannot be conveyed (neologisms). There may be repetition of the same word or phrase at great length, as if it had magical properties or held the secret of the universe.

NEAR-DEATH AND NEAR-BIRTH EXPERIENCES

The near-death experience (NDE) is an altered state of being which can be accessed in various ways, including through ketamine use, which can produce every feature of an NDE (Jansen In press; 1997a; 1996a, b; 1989; Ghoniem et al. 1985; Rogo 1984). In 1973, an anaesthetist was given ketamine i.v. in a lung research study:

> I had no warning. I heard a dull buzzing and then, within seconds, I was unconscious. . . . I was a mind suspended in space. . . . I was not afraid, I was more curious. 'This is death. I am a soul, and I am going to wherever souls go . . . ' (Johnstone 1973).

An NDE does not necessarily mean that the person is physically near death. This is usually not the case, and ketamine does not stop the heart. There may be a belief that awareness has left the body and traveled through a tunnel towards light; the conviction that one has died; apparent communion with God; apparently entering other realities; emergence of old memories; a life review; euphoria; fear; ringing/buzzing/whistling sounds followed by travel at high speed; inability to feel pain; clarity of thought; and visions of landscapes, angels, people, and religious and mythical figures. Rather than paradise, it is also possible to emerge into Hell. The loss of contact with external reality and the sense of being part of other, more fundamental realities may be overwhelming. The experience can be split into phases. Like the NDE, ketamine can also produce very abrupt shifts in the mind, as if a switch has clicked. Some people who had an NDE during an emergency have described their resuscitation in detail (Sabom 1982). Many surgical patients (especially those given ketamine) have also reported what was said and done during the operation, although they appeared to be unconscious (Schwender et al. 1997). "Hovering above the scene" is a typical ketamine effect.

Some NDEs may involve reexperiencing the birth process in symbolic form. Grof (1988) was one of those who suggested that in the pre-birth "amniotic universe" there are no boundaries and no time. Reexperiencing adults may interpret regressing to this level as an ocean or the galaxy (for example), perhaps developing into an experience of cosmic unity. The feeling of "coming home" relates to this level, a "return from exile." In the original birth process, the prebirth "paradise" is then disrupted by uterine contractions, but the cervix is closed so there is no way out. Contractions restrict the blood supply, producing the same chemical conditions in the brain that may trigger an NDE in later life. The symbolism of the NBE is of engulfment and imminent disaster, the beginning of the hero's journey, expulsion from Eden and the experience of no exit or Hell: entrapment in a claustrophobic, endless nightmare from which escape is impossible. The person is cut off by the contractions from outside contact. The contractions continue but the cervix dilates and the baby moves through the birth canal, struggling against suffocation and compression, with energy building up towards explosive release. There may be images of cataclysmic events, and the struggle may have sexual, aggressive, demonic, and "fire" elements when it is reexperienced. This build-up of tension is followed by release as the child is born from the darkness into light. The successful rebirth in the reexperiencing adult may involve visions of white or golden light, beautiful vistas, a sense of salvation, death and resurrection, arrival in paradise, God, and the self reuniting with the divine source in the universal energy. The different stages may not be worked through sequentially, and any stage may be repeated many times. There are ketamine experiences matching all aspects of this model. Some prominent psychoanalysts have

claimed to regress clients without drugs to the prebirth level (e.g., Winnicott 1958), and the fetus can hear and remember sounds heard from 20 weeks after conception (Evans 1998) as perception and memory develop in areas once thought to be too primitive (e.g., the thalamus). As the NDE often has therapeutic sequellae, this suggests that safe induction of the NDE using ketamine may have therapeutic value. Ketamine treatment has been used with good results in alcohol dependence (Krupitsky & Grinenko 1997).

Brain cells bathe in dissolved salts that may wash in and out through tunnels in the cell wall. Ketamine binds to PCP receptors inside some of these tunnels and causes a blockage (Thomson, West & Lodge 1985). Glutamate crosses the gap between cells and binds to NMDA receptors on the other side (on the cell surface) turning the chemical key in the lock, but while the tunnel is blocked by ketamine binding to PCP receptors, no new impulse can be fired. Confusingly, the term "NMDA receptor" is often loosely used for the whole complex, including the PCP receptor (Cotman, Monaghan & Ganong 1988). Ketamine also affects opioid, dopamine (it activates dopamine systems), serotonin, noradrenaline, nitric oxide, sigma, GABA (gamma amino-butyric acid, an inhibitory messenger), and the acetylcholine and endocrine systems, among others (e.g., detailed review in Jansen In press; Lindefors, Barati & O'Connor 1997; Hustveit, Maurset & Oye 1995; Oyama, Matsumoto & Kudo 1970). These other systems may be considered when the effects of the drug are interpreted, e.g., kappa opioid receptors may contribute to the psychedelic effects (Hirota & Lambert 1996; Pffeifer et al. 1986). While ketamine produces NMDA receptor blockade, subanaesthetic doses may, in some tracts of the brain, actually release glutamate (Anand et al. 2000; Moghaddam et al. 1997) resulting in excitement via non-NMDA glutamate receptors such as kainic acid and AMPA receptors. At subanaesthetic doses, blocking the NMDA receptor complex also does not result in a "switched-off brain" because the switched-off cell may have been one which releases the inhibitory GABA. If inhibition is removed, the next cell in the chain becomes excited (Drejer & Honore 1987). Thus the neocortex is "hot" (hypermetabolic) in brain scans at psychedelic ketamine doses (Vollenweider et al. 1997a, b). At high doses, the brain is more likely to be calm, as in conventional anesthesia.

Both NDEs and ketamine experiences involve blockade of the NMDA receptor complex (Jansen 1989). Many factors, such as a sudden fall in oxygen or blood sugar, a rise in carbon dioxide (e.g., due to interruption of the blood supply during a heart attack), or other spontaneous factors cause a flood release of glutamate (Benveniste et al. 1984). This overexcites brain cells which die, bursting like overinflated balloons (this is termed excito-toxicity; Rothman & Olney 1987). Ketamine can prevent this brain damage via the same mechanism which is central to its psychedelic effects: blockade of tunnels so that "the sea" of ions cannot rush in (Weiss 1986). This led to the prediction that the brain would have a natural protective mechanism against the glutamate flood (Jansen In press; 1997a; 1990a; 1989), probably a counter-flood of natural NMDA receptor complex blockers, producing ketamine-like NDE effects. While a person is having an NDE, the brain is thus protecting itself from excito-toxic damage. The existence of such natural glutamate blockers is now established. These include NAAG (N-acetyl-aspartyl-glutamate), magnesium and kynurenic acid, all of which protect cells from excito-toxic damage (Coyle 1997; Miranda et al. 1997; Feldman 1996). The endopsychosins, once claimed to be natural NMDA receptor blockers, (Jansen 1990a) proved to be a mirage.

Those who were oxygen-deprived for long periods and had profound NDEs sometimes survived with unimpaired brains. This lack of damage may result from a very effective inherited mechanism for blocking overexcitation. Those who can have an NDE may be less likely to suffer brain damage (Jansen 1997a). These may be the same group who report psychedelic experiences with ketamine. About 40% of the population have had some form of NDE, when the widest possible definition is used including NDE-like phenomena during dreams (Sabom 1982). The percentage who report emergence (i.e., psychedelic) phenomena after ketamine anesthesia also averaged about 40% across many studies. Dreams, ketamine journeys and NDEs are all states in which there is a reduced input from the outside world. Those who do not recall their dreams are also unlikely to recall ketamine journeys. In a study of 150 patients, 45% recalled dreaming at home (Hejja & Galloon 1975). Of these home dreamers, 75% described dreams during ketamine anesthesia (50 out of 68), while only two of the 82 who were not home dreamers had dreams during the anesthesia. The percentage of home dreamers is about the same as the percentage reporting emergence phenomena in many anesthetic studies: about 40%. Genetic differences may be responsible (e.g., Malhotra et al. 1998).

The same altered state of being may be reached by many different routes. The above glutamate hypothesis does not apply to every NDE, nor is it incompatible with a belief in "life after life" as it limits itself to bodies that have not permanently ceased to live. The production of an NDE with ketamine does not necessarily diminish the meaning and value of the experience.

Ketamine blocks out the outer world, and sensory deprivation itself can result in out-of-body experiences (Lilly 1978). In many near-death situations, sensory input is cut off, isolating parts of the brain from the setting. The now empty stage of awareness fills with new realities originating from the depths of the mind. The NMDA receptor is the link joining NDEs, Lilly's "tank-trips" and ketamine journeys together. Memories may be suppressed by a gate that admits external signals when we are concentrating upon an external task. If this input is cut by a sensory

deprivation tank, ketamine use, sleeping, a heart attack, or a spontaneous mental event (epileptic attacks can arise in a person at rest), for example, and combined with inner stimulation, stored memories and other material may be released and organized into a semi-meaningful drama . This has evolutionary value if the message received is: "it is not your time to die, go back!" or the reinfusion of a person's life with a sense of meaning, leading to improved health (Krupitsky & Grinenko 1997). NMDA receptors, a part of this gate, are dense in areas of the brain where data from the external world are integrated with the inner world (Jansen, Faull & Dragunow 1989).

TOXIC EFFECTS

The use of ketamine has been linked with a wide range of mental health problems including anxiety, panic attacks, flashbacks, posttraumatic stress disorder, persistent perceptual changes, mania, depression, suicide, insomnia, nightmares, night terrors, an unpleasant feeling of being unreal or that the world is unreal, paranoid delusions, persistent hallucinations, automatic behavior, fragmentation of the personality and aggression (Jansen In press). However, a cause-and-effect relationship has usually not been established in these cases. Some people will develop mental health problems regardless of any drugs they may have used. Establishing that a drug actually causes a problem, rather than being linked with it by chance, can be difficult. Nevertheless, brief case reports often boldly conclude that taking a drug caused a particular condition, and the sufferer aids this process by seeking external explanations and making false attributions. There is a natural reluctance to accept that something would have gone wrong "internally" in any case, or may have already been wrong. In Victorian times, favorite "roots of all evil" in this sense, given serious discussion in the medical literature of the time, were railway and bicycle travel and masturbation. Bearing this caution in mind, let us now consider the possibilities.

Freudian theory maintains that anxiety-provoking material unacceptable to the waking mind is repressed into the unconscious. If defenses against this disturbing material are impaired by taking ketamine, the outcome will partly depend on the set and setting. The indirect blockade of NMDA receptors is one reason why so little of a ketamine experience is remembered. The same mechanism is involved in the failure to recall dreams, except that a natural blocker is involved: a "mental fire wall" which obliterates awareness of other realities incompatible with our ordinary reality. Breaches in these barriers may not wholly self-repair as the acute effects of the drug resolve, resulting in some types of material gaining increased access to the conscious mind. This can result in a variety of mental health problems. One of these simply involves an increased level of imagery and some lack of focus. This is called Pandora's box syndrome (Jansen 1997b). The imagery is intensified by anxiety. During a ketamine experience itself, breaching the walls can have results as follows:

> I felt excruciating aversion, fear. . . . It seemed to me that I would never get out of this nightmare, that I was slowly and painfully dying, that I, my entire self, would melt in this black mass, but my brain would go on working. That I would feel, think, not live, but suffer. . . . Everything I saw resulted from my hopeless life. . . . As if the trash accumulated in me during years and years went out of me during an hour. I do not want it to repeat, I am afraid of this nightmare . . . I would never forget it. . . . (Krupitsky & Grinenko 1997).

> I was alone in my room. . . . Then it was in with the i.v. hit while sitting at my desk . . . The next thing I remember is extreme panic. I was convinced that I had discovered THE SECRET . . . that this world we live in now is an illusion and I had seen the Real Universe. The Gods could not possibly let me live with this forbidden knowledge. I knew that I was about to die. This was all very fast, a matter of seconds. I . . . tried to decide if I should rush out of the apartment into the corridor screaming for an ambulance. Fortunately I decided that this was futile. My death was seconds away and I should lie on my bed and wait for it, which I did. My heart must have been going about 200 a minute. 30 seconds later I was perfectly O.K. . . . (Interview from Jansen In press).

The fear of being killed for stealing forbidden knowledge from the Gods is closer to Jungian psychology, an archetypal mythical experience, and can be related to Grof's model of the near-birth experience.

> I went to Hell instead. I took the largest dose ever, 200mg as a shot in the buttock, and curled up for the night. Once again I was going through a pipe system, but this time I came out into a small, dimly lit red room, and was filled with terror. I had lost my body and had become something resembling a dwarf's hood hanging on a peg. I know that sounds funny, but I thought that I would have to stay forever in that room on that hook. I was in HELL. I screamed, and screamed . . . it was my first experience of what ETERNITY really means. I almost became a Catholic the next morning. That experience seriously shook the basis of my disbelief. I thought that people were absolutely mad who wanted to carry on for Eternity without their bodies. It made me fervently hope that the end really is the end . . . (Interview from Jansen In Press).

Depersonalisation refers to feelings of being unreal, detached and unable to feel emotion. *Derealisation* is where the setting appears to be unreal, a cardboard stage-set. Both are deeply unpleasant and occur as adverse ketamine effects.

Attention, learning and memory are altered during ketamine experiences (Curran & Morgan 2000; Malhotra et al. 1996). This is partly due to blockade of NMDA receptors (Cotman, Monaghan & Ganong 1988) but acetylcholine is also important in memory (Bartus, Dean & Flicker 1987) and ketamine has anticholinergic properties (Hustveit, Maurset & Oye 1995; Morita et al. 1995). The loss of acetylcholine in Alzheimer's disease is one of the most distinctive features of the condition, as is loss of

glutamate (Bartus, Dean & Flicker 1987). Ketamine has been used to produce a model of Alzheimer's disease (Ellison 1995).

Research into cognitive problems which persist once the urine is proven to be free of all drugs and their metabolites is rare, and coexisting depression and anxiety (which affect memory and concentration) must be excluded as causes of these problems. Curran and Morgan (2000) found a persistent semantic memory problem in a group of 19 people at three days after recreational ketamine use, but it is possible that norketamine would still be present in significant quantities at this stage. Norketamine is also an NMDA receptor antagonist (Ebert et al. 1997), with far less tendency to produce hallucinogenic effects. Patients can tolerate prescribed oral ketamine long-term for chronic pain (Humphries, Melson & Gore 1997). Thus the resolution of hallucinogenic effects does not imply that there is an inadequate level of active metabolites remaining to affect cognitive function. The pharmacokinetics of norketamine in polydrug-using adults aged 20 to 30 is an area requiring further study.

In one example, an anesthetist became dependent on ketamine and had problems with memory, attention and concentration, and a subtle change in visual perception persisting into drug-free periods (Jansen 1990b). Ketamine use would be followed by impaired recall and difficulty with word finding. The visual change involved mildly increased graininess, aggravated by fatigue, anxiety and other drugs. This is a persistent perceptual change, differing from a flashback as it is chronic rather than episodic. Neurons undergo many changes throughout life, forming the basis of some types of memory and of the brain's compensation for aging. NMDA receptors play a key role in this plasticity. Chronic ketamine administration in animals blocks this plasticity (Corbett 1990), but there is no evidence that ketamine causes brain damage at the cellular level in primates (human/monkey), although changes do occur in rat brains. Administraion of 40mg/kg results in vacuoles (fluid-filled bags) appearing within cells in some parts of the rat brain, such as the cingulate gyrus, which resolve after several days. High, repeated doses of the more toxic PCP or its even more toxic relative MK801 (dizocilpine) can result in some cell death (Olney et al. 1991; Olney, Labruyere & Price 1989). Auer and colleagues (1996) injected monkeys with MK801, the most toxic drug of this group (never approved for human use) and were unable to produce any toxic changes. Humans and monkeys are not at risk of these changes because of differences in metabolism between rat and primate brains. Ketamine can block excito-toxicity (brain damage due to low oxygen etc.) but it can also excite the brain at low doses by switching off the inhibitory system. This is not damaging in primates because ketamine also binds to a wide range of receptors which shut down this form of excitement before structural damage can result. Ketamine's promiscuity greatly improves its safety relative to MK801, which binds very specifically to the NMDA receptor complex. Rats have rates of brain metabolism which are twice as high as primates to start with. It is because of this higher base rate of excitement that ketamine causes over-excitement in rats at doses below those at which it activates shut-down systems. NMDA receptors must be blocked for at least two hours to cause reversible changes and at least 24 hours to produce some cell death, but ketamine has a short half-life (about 20 minutes in rats) so many injections are needed, over a prolonged period, to produce persistent change (Farber et al. 1998). Reversible toxic changes in the rat brain appear at 40mg/kg of ketamine and stop at 100mg/kg, with no further changes (Sharp et al. 1994). Attempts to produce toxic changes in monkeys were a total failure at 10mg/kg i.m. ketamine (Sharp 1998).

Thus humans and monkeys are protected from toxic changes by the rising anesthesia, which cuts in above a certain dose and calms cells down. This also happens in rats, hence the 100mg/kg plateau, but it happens too late to completely avoid some toxic changes as rats are already "running hot" because of their twice as fast metabolic rate. Cell changes do not appear if rats are pretreated with a wide range of drugs, including LSD and amphetamine-like substances such as DOM (4-methyl-2,5-dimethoxy-amphetamine) (Farber et al. 1998), all the benzodiazepines and barbiturates, anti-cholinergics (Olney 1994), antipsychotic drugs including haloperidol, clozapine and olanzepine (Farber et al. 1996), nifedipine and other drugs. Some of these block toxic changes in rats by switching inhibitory systems back on again, and ketamine itself activates these inhibitory systems at higher doses. It has been suggested that the process which is neurotoxic in rats is responsible for psychedelic effects in humans, and may be involved in schizophrenia (Farber et al. 1998). However, most of the drugs which block toxicity are not treatments for schizophrenia (e.g., LSD), nor is it proven that these drugs will block ketamine effects in humans. For example, lorazepam reduces emotional distress but not ketamine psychosis (Krystal et al. 1998). Nevertheless, many anecdotes indicate that LSD and amphetamine-like substances (MDMA, 2,5-dimethoxy-amphetamine or 2CB, etc.) when taken 90 minutes prior to ketamine, reduce dissociation (e.g., Turner 1994). The resulting state is less intense than either drug taken on its own, differs from either drug, and is much easier to fully recall than a pure ketamine experience.

Although examination by a neuropathologist may find no structural cell changes, there is increasing appreciation of the role of much smaller entities in memory, such as the response of immediate early genes which produce "third messengers" such as the c-Fos protein (Dragunow et al. 1989). Subanaesthetic doses of ketamine induce formation of c-Fos (Nakao et al. 1996) but full anesthetic doses may not (Nakao et al. 1993). The dopamine/glutamate mutual regulation system is involved in this process.

Repeated chronic doses of ketamine result in persistent alterations in the dopaminergic system, among others (Lindefors, Barati & O'Connor 1997; Irifune, Shimzu & Nomoto 1991), and these alterations will have feedback effects on glutamate systems (Verma & Moghaddam 1996) that might result in a loss of efficiency in memory systems that is not apparent as a change in cell structure. Thus changes may not only occur at the receptor level (Morita et al. 1995; Williams, Dichter & Molinoff 1992) but also at the level of intracellular signaling and nucleic acid activation/deactivation. This phenomenon has been investigated for cocaine, with which ketamine shares important properties (e.g., Nishimura & Sato 1999). In response to chronic cocaine, induction of Fos-type immediate early genes is down regulated, resulting in persistent changes downstream in such gene products as the AP-1 transcription factor (Hope 1998).

Of a group of women undergoing elective surgery, half had droperidol and fentanyl, and the other half diazepam and ketamine. The droperidol/fentanyl group complained of restlessness, dysphoria and fatigue after the operation. No complaints were made by the ketamine/diazepam group. At three months, the only significant difference between the two groups was that 25% felt that their memory and concentration were severely affected by the droperidol/ fentanyl, versus none for the ketamine /diazepam group. There was no difference in dreaming, nightmares, hallucinations or illusions. Does a single dose of droperidol/ fentanyl really cause lasting memory impairment? The women disliked these drugs at the time of the surgery, and this dislike made them more inclined to blame the anesthesia for problems they were having three months later, rather than considering other causes (Klausen, Wiberg-Jorgensen & Chraemmer-Jorgensen 1983).

After a binge, there is a gradual return to normal mood over several days as the slow decline in norketamine levels provides a cushioning effect. Being too high is more likely than being too low, and ketamine may trigger mania in bipolar disorder (manic-depression), as it has a specific chemical action that reverses that of the mood-stabilising drug lithium (Dixon, Los & Hokin 1994). However, there are anecdotal indications that, as with other stimulants, a low mood may still follow the high but it does not appear for about a week. Ketamine has antidepressant effects (Berman et al. 2000). However, amphetamine can also be described as an antidepressant, although its use is followed by a period of low mood (a crash), usually the following day, while low mood after MDMA appears mid-week (Jansen 1997b). Suicidal actions while a person is affected by ketamine may not always be due to low mood. In a group of 23 users, half reported a lasting elevation in mood; there was an equal division between positive and negative effects, with 30% noting deeper insights (Siegel 1978).

Ketamine flashbacks have been defined as episodes lasting for a few seconds in which the user reexperiences some mild phenomena (White & Ryan 1996). This differs from the media view that a flashback is a complete, unprovoked reliving of a drug experience. A drug-specific, physical brain effect is an unlikely explanation as a wide range of drugs, with quite different actions in the brain (e.g. LSD, ketamine and MDMA) are implicated (Jansen 1997b), and flashbacks also occur in posttraumatic stress disorder (PTSD). This is a delayed response to an exceptionally stressful event (World Health Organization 1992). Ketamine experiences can be exceptionally stressful, so some flashbacks following traumatic "K-trips" may actually be PTSD, which involves a repeated reliving of the trauma in the form of intrusive memories or dreams, may include episodic hallucinations, appears after a latency of a few weeks, and can also involve problems with memory, learning, attention, anxiety and depression (Van der Kolk 1997). Post-LSD flashbacks are more likely after traumatic LSD trips (Strassman 1984). Some drug-related flashbacks may be a form of conversion disorder (hysteria), where anxiety and other forms of psychological distress are converted into symptoms such as perceptual change, somatic symptoms, amnesia and others. Dissociative drugs are especially likely to trigger such symptoms, and conversion disorder (hysteria) is classified as a dissociative disorder. This disorder is a partial or complete loss of integration between memories of the past, awareness of identity, immediate sensations and control of movements (World Health Organization 1992), all of which are major acute effects of ketamine. Ketamine can give rise to dangerous automatic behavior, with activities continuing out of contact with the observing ego (e.g., repeatedly walking into a wall). Siegel's study of 23 recreational users noted a high incidence of flashbacks (and attentional dysfunction), but the definition of flashbacks used in this study was not stated (Siegel 1978). Large, controlled anesthetic use studies conclude that ketamine is usually devoid of significant persistent effects once the drug and its metabolites have cleared the body (Schorn & Whitwam 1980; Modvig & Nielsen 1977).

Ketamine use has been linked with sleep disorders such as sleep paralysis and night terrors. The sleeper wakens from deep stage four sleep with a loud scream and may report being either trapped in a small space or in a place without coordinates. These are not nightmares as they do not arise during the normal dream REM periods. For example, a woman had "a trip to Hell" on ketamine, and screamed very loudly. Several weeks after stopping ketamine, the night terrors began. They continued for several years, stopping when she was taking drugs (including alcohol), and restarting when she had been drug free for several weeks. The condition gradually faded. The screaming may have ceased during periods of drug use as these provided a conduit for buried parts of the psyche to communicate with the surface in other ways. When she stopped using drugs, these parts may have been "entombed" and only burst through during deep sleep by means of a

penetrating scream. Nevertheless, the wall-weakening effect of the initial ketamine may have triggered the condition. There were predisposing personality features and a family history of mental health problems (Jansen In press). Ketamine may have also disrupted the wetware/software of sleep mechanisms (Feinberg & March 1995).

There are rare reports of prolonged hallucinations following ketamine anesthesia, but as there was no normal period before the onset of the hallucinations, these are not flashbacks. Hallucinations continued for five days in a boy who was given ketamine during investigations of brain-based symptoms. He had preexisting abnormal brain waves over the visual cortex, raised pressure in his brain, severe headaches, loss of appetite, vomiting, fever and nausea. He was then given ketamine without after-effects. Ten days later, he was given ketamine again and had a scan involving injection of air into spaces in the brain. This was followed by five days of hallucinations typical of delirium (Perel & Davidson 1976). It seems unlikely that ketamine was responsible, especially as operations are often followed by delirium for a few days.

In one study, 1,400 patients were given full surgical doses. There were three cases of prolonged hallucinations, the longest being for three weeks. In no case did hallucinations begin after a period of normality (Fine & Finestone 1973). In another study of over 200 patients, the mental changes following ketamine were compared with those of other anesthetics. Tests were carried out repeatedly for a year. There were no differences between the groups in mental performance, hallucinations and behavior. Multiple doses did not cause persisting impairment of intellectual function or personality (Abajian, Page & Morgan 1973). In another study, ketamine or halothane gas was given to 100 children; one month later, there was no difference in emotional disturbances between the groups (Modvig & Nielson 1977). Schorn & Whitwam (1980) concluded that ketamine was unlikely to cause permanent changes in personality or intellect. These anesthetic studies are much larger and much better controlled that the studies which exist of recreational users (Curran & Morgan 2000; Jansen 1990b; Siegel 1978). However, the patient usually receives the drug at a full anesthetic dose, possibly with effect modifying drugs such as diazepam, droperidol and propofol, and probably not more than 20 times. Subanesthetic doses have different effects from full anesthetic doses, and are, paradoxically, more likely to have adverse effects on mental health for the reasons discussed previously. Subanesthetic doses produce metabolic hyperfontality like that seen in schizophrenia with positive features (Vollenweider et al. 1997a, b) rather than a calm brain, and there is actual activation of glutamate (Anand et al. 2000; Moghaddam et al. 1997), while full anesthetic doses lead to a fall in extracellular glutamate levels (Rozza et al. 2000). This raises a question mark over the degree of reassurance which can be taken from anesthetic studies when we shift our attention to psychedelic use.

A ketamine trance can resemble catatonic schizophrenia. The eyes may rove from side to side and limbs move in semi-purposeful ways, while the mind stages an intense inner drama. Some people will suddenly sit up, speak a phrase, and lie down again. Ketamine users often insist that events "really happened" and that the drug is merely a key for doors to "other realms." Most of these people are not insane, just as persons who regard their NDEs as real are not usually insane. However, frequently experiencing these other states of being may result in problems back in "ordinary reality" if the borders between them become blurred. This lack of boundaries between realities, the interpenetration of one by the other, may be distressing and can meet diagnostic criteria for psychosis. Marcia Moore repeatedly warned that "this delusion of grandeur thing has to be watched" and on at least one "journey" she described herself as "briefly but certifiably insane."

In some types of schizophrenia, certain glutamate-releasing cells and/or terminals are missing and there is an excess of dopamine. This is probably due to genetic and prebirth factors (Moghaddam 1994). The net result may be similar to blocking NMDA receptors while stimulating dopamine release—the effects of ketamine. The results of subanaesthetic doses have been interpreted as being similar to the positive (hallucinations, delusions, disordered thinking), and the negative and cognitive (emotionless, apathy, isolation, concrete thinking, absence of thought, impaired memory /attention /concentration / planning/task completion) symptoms of schizophrenia (Adler et al. 1999; Carpenter 1999; Krystal et al. 1994). However, normal subjects who were given ketamine did not hear critical voices, also a weakness in LSD models of schizophrenia. The studies at Yale used very general terms such as "conceptual disorganization" and "unusual thought content," and it seemed that the "dream-like states" of the 1960s had been reframed as "schizophrenia-like symptoms" in the 1990s using very broad criteria. However, ketamine was then given to persons with schizophrenia and a specific, acute worsening of their schizophrenic symptoms was noted, strengthening the theoretical basis for the model—although ketamine-induced "symptoms" in controls were distinctly different from the ketamine-induced symptoms in persons with schizophrenia (Malhotra et al. 1997; Lahti et al. 1995). While the model is flawed, and apparently traveling down tunnels at high speed into light is not really a feature of schizophrenia, these studies may eventually lead to new and better treatments for people in distress. These studies have already led to new drugs with pro-glutamate, anti-ketamine effects (e.g., Arvanov & Wang 1998).

A true drug-induced psychosis is one that is not explained by another underlying condition, and which persists once the urine is clear of drug metabolites (Poole & Brabbins 1996). In some heavy daily users, norketamine can take several days to leave the body. John Lilly rapidly

became nonpsychotic after being cut off from his drug supply, and was never in hospital for long except when he had serious physical injuries. "Ketamine intoxication with paranoia" may be a better description for his episodes than "drug-induced psychosis," which is one where the psychosis starts during intoxication and is still present when the urine is clear of metabolites. It should only recur on reexposure to the drug and not at any other time, and must have a different course and outcome from schizophrenia, bipolar disorder (manic-depression) and related conditions (Poole & Brabbins 1996). Some doubt that any drug can produce such a condition. Connell's famous report on amphetamine psychosis concluded that this only occurred with intoxication and resolved as the urine cleared of metabolites, a process taking up to a week in some people (Connell 1958). Where it does not resolve, long-term follow-up usually finds schizophrenia, bipolar disorder or a related condition. Lilly had many features of schizotypal disorder existing years before he took ketamine (Lilly 1978). Ketamine increases schizophrenic symptoms while a person with this disorder is affected by the drug, but the symptoms are not increased once the drug and its metabolites have left the body (Malhotra et al. 1997; Lahti et al. 1995). Hence some anesthetists argue that ketamine can be safely used with those having schizophrenia (Ishihara 1997).

PHYSICAL EFFECTS OF KETAMINE

At psychedelic doses, ketamine can behave more like a stimulant than a sedative and usually increases the heart rate (White & Ryan 1996). Movement in animals is strongly stimulated by low doses, after recovery from the trance (Irifune, Shimzu & Nomoto 1991). Deaths by pure overdose (OD), i.e. in the absence of other drugs, especially alcohol, serious medical and surgical problems, or an idiosyncratic reaction (i.e. not dose related) are exceptionally rare. Of 87 ketamine-linked deaths in New York City examined in one study, none was purely due to the use of ketamine (Gill & Stajic 2000). The Parke-Davis company has reported that there are cases of accidental injections with ten times the amount required for surgery, with no obvious, lasting effects (Parke-Davis 2000). Of two known deaths by pure ketamine overdose, one was described as "a homicide for homosexual ends" (Licata, Pierini & Popoli 1994) and the other was a woman of 49, a New Age company owner, who took ketamine daily for seven months. She believed that she had an angel lover on the other side who sent her messages (e.g., by forming clouds into heart shapes). One day she put on her finest clothes, lay down on her bed, and took a huge ketamine overdose so that she could join her angel lover. At postmortem, she weighed six stone (84 pounds) and had a minimum of 600mg of ketamine per litre of blood (Jansen In press).

Overdose is a relative term. A club "bump" of ketamine would be a serious underdose for surgery. Some people consider any psychedelic drug use to be an OD as the mind is no longer within the usual limits of normal. Those who take ketamine in clubs and can no longer walk are sometimes described in the media as having collapsed and overdosed. They may be rushed to hospital as emergencies, while patients in those same hospitals may be given doses ten times higher as an anesthetic. To decide the OD dose, we need to consider the purpose for which it is intended, the location, the route (mouth, nose, vein, muscle), the user (age, size, sex, tolerance, health), other drugs taken and other factors. The top end of the medical range is 13mg/kg i.m., and psychedelic doses rarely exceed 2mg/kg i.m. Although overdose has often been mentioned in the literature of street drug agencies, in nonmedical use the real physical dangers arise mainly from the setting as ketamine can leave the taker in a helpless and/or confused state (Jansen 1993). Difficulty with balance, combined with numbness, muscle weakness and impaired vision, has resulted in falls which were sometimes lethal. The analgesia has resulted in severe burns, and lying down has resulted in ulnar nerve compression in the arm where the body was lying on it (Jansen In press). Other risks from the setting are drowning, death by hypothermia from lying outside in winter, traffic accidents and becoming a crime victim (e.g. "sedate rape"). D.M. Turner died in 1997 at age 34, having drowned in a bathtub with a bottle of ketamine at his side. He appears to have collapsed into the water, after ignoring his own harm minimization advice about not injecting alone while engaged in activities such as bathing (Turner 1994). This accidental death illustrates the dangers of becoming helpless in settings other than lying down on a bed.

Some of the physical effects of principal concern in a nonmedical use context are difficulty with walking and balance resulting in falls, numbness, slurred or hoarse speech, dizziness, visual problems, vertigo, nausea and vomiting, headaches, sweating, muscle spasms, and twitches, sudden jerky movements and tremor (Hefez & Lanyi 1972).

There is a risk that rapid i.v. injection will suppress breathing (Zsigmond 1976), although ketamine does not usually suppress breathing when injected into a muscle in an adult, and swallowing and airway reflexes are usually preserved (Parke-Davis 2000). Airway problems have occurred at surgical doses in very rare cases (Taylor & Towey 1971). There are very rare cases of children who failed to breath for a minute or more following i.m. surgical doses (Green et al. 1998; Smith & Santer 1993). Snorting powders can damage the linings of the nose, while injecting carries a risk of infections.

K Pains are severe abdominal pains commencing after high dose, daily use (Jansen In press). They can feel like severe gas pains, but much worse. They tend to appear

when the intoxication resolves. These pains are mysterious because among patients with severe head trauma who need deep sedation, ketamine is said to be the pain killing drug of choice specifically because it does not cause gastrointestinal motility disorders (Zielman & Grote 1995). These pains may be irritable bowel syndrome triggered by the psychological changes discussed previously.

Movement disorders are possible. A 20 year old, experienced user gave himself an i.v. injection. Ten hours later he attended a hospital with his tongue sticking out, rigid and pointing to the left, and his neck bent backwards and to the left because of muscle spasm (dystonia). He was unable to speak but could still write. He was given i.v. diphenhydramine, resulting in symptom relief within three minutes (Felser & Orban 1982). There are rare reports of ketamine both causing epileptic fits (Thompson 1972), and stopping fits (Sybert & Kyff 1983). The reported "fits" may have been a misinterpretation of other ketamine effects: a sudden trance, abnormal movements or collapse, and disorientation with agitation (Kugler & Doenicke 1994). Whether ketamine is a pro- or anticonvulsant is an old controversy; it may be both. While a person is affected by ketamine, there may be blurred or double vision, roving movements of the eye, and possibly raised pressure within the eye in some cases (Antal, Musci & Faludi 1978). Rare side-effects include problems with the sclera and conjunctiva, and swelling around the eyes. Abnormalities in other parts of the eye were noted in some animal models but it was shown that another drug given at the same time, called xylazine, was responsible for some of the toxic changes (Calderone, Grimes & Shalen 1986).

Most studies report no impairment of immunity, but the issue is not settled (e.g., Nishina et al. 1998; Krumholz et al. 1995). In very rare cases, ketamine has been linked with a marked rise in temperature (Zsigmond 1971) but this is also controversial (review: Dershwitz, Sreter & Ryan 1989). There have been rare cases where the heart rate fell and of problems with the heart rhythm (see a review in White & Ryan 1996). There is a modest rise in blood pressure (after i.v. injection) normalizing within 20 minutes, but no evidence of damage as a result. Higher doses do not raise the pressure further. People with high blood pressure are not at greater risk of post-ketamine pressure rises. There have been very rare cases of dramatic rises unrelated to dose, and of low blood pressure (Tomlinson 1994). (The issue of ketamine dependence will be reviewed separately.)

The relevance of the PCP literature to ketamine studies is controversial, and this literature should not be over-cited. PCP is much longer acting than ketamine, has a much higher affinity for the NMDA receptor, is significantly more toxic, is no longer used in medicine and is far more likely than ketamine to produce toxic changes in rat brain cells (Olney et al. 1991; Olney, Labruyere & Price 1989).

CONCLUSIONS

There are indications from a variety of sources that nonmedical use of ketamine has increased in the last 15 years, linked with the growth of the dance culture and alternative spirituality movement. The drug has many psychedelic effects. It is important that those who are involved in the treatment of ketamine-related problems understand the reasons why this drug is taken, and have a realistic understanding of the possible adverse effects. The view that ketamine is a drug only taken by masochistic, bored "space cadets" who seek bad trips (an impression created by some media reports and drug agency leaflets) is far too narrow. The drug provides new insights into aspects of the brain/mind interface such as the NDE and dreaming, and also into human disorders such as schizophrenia and Alzheimer's disease. The psychedelic effects may have therapeutic value in some cases, and be harmful in others.

REFERENCES

Abajian, J.C.; Page, P. & Morgan, M. 1973. Effects of droperidol and nitrazepam on emergence reactions following ketamine anesthesia. *Anesthesia and Analgesia; Current Researches* 52: 385-9.

Adler, C.M.; Malhotra, A.K.; Elma, I.; Goldberg, T.; Egan, M.; Pickar, D. & Breier, A. 1999. Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. *American Journal of Psychiatry* 156 (10): 1646-49.

Ahmed, S.N. & Petchkovsky, L. 1980. Abuse of ketamine. *British Journal of Psychiatry* 137: 303.

Anand, A.; Charney, D.S.; Oren, D.A.; Berman, R.M.; Hu, X.S.; Cappiello, A. & Krystal, J.H. 2000. Attenuation of the neuropsychiatric effects of ketamine and lamotrigine: Support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Archives of General Psychiatry* 57: 270-76.

Anonymous. 1997. Ketamine: The hot new drug of abuse. *Forensic Drug Abuse Advisor* 9 (6): 10-20.

Antal, M.; Musci, G. & Faludi, A. 1978. Ketamine anesthesia & intraocular pressure. *Annals of Opthalmology* 10: 1281-89.

Arvanov, V.L. & Wang, R.Y. 1998. M100907, a selective 5-HT2A receptor antagonist and a potential antipsychotic drug, facilitates N-methyl-D-aspartate-receptor mediated neuro-transmission in the rat medial prefrontal cortical neurons in vitro. *Neuropsychopharmacology* 18 (3): 197-209

Ashley, R. 1978. Avant-garde highs. *High Times* 31: 62-64.

Auer R.N.; Coupland, S.G.; Jason, G. W.; Archer, D.P.; Payne, J.; Belzberg, A.J.; Ohtaki, M.& Tranmer, B.I. 1996. Postischemic therapy with MK-801 (dizocilpine) in a primate model of transient focal brain ischaemia. *Molecular and Chemical Neuropathology* 29 (2-3): 193-210.

Australian Bureau of Criminal Intelligence. 2000. *Australian Illicit Drug Report 1998-99*. Canberra, Australia: Australian Bureau of Criminal Intelligence.

Australian Bureau of Criminal Intelligence. 1995. *Australian Illicit Drug Report 1994*. Canberra, Australia: Australian Bureau of Criminal Intelligence.

Bartus, R.T.; Dean, R.L. & Flicker, R.C. 1987. Cholinergic psychopharmacology: an integration of human and animal research on memory. In: H.Y. Meltzer (Ed.) *Psychopharmacology: The Third Generation of Progress*. New York: Raven Press.

Benveniste, H.; Drejer, J.; Schouseboe, A. & Diemer, H. 1984. Elevation of extracellular concentrations of glutamate & aspartate in rat hippocampus during cerebral ischaemia monitored by microdialysis. *Journal of Neurochemistry* 43: 1369-74.

Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S. & Krystal, J.H. 2000. Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* 47 (4): 351-54.

Borgbjerg, F.M.; Svensson, B.A; Frigast, C. & Gordh, T. 1994. Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: A light and electron microscopic examination. *Anesthesia and Analgesia* 79 (1): 105-11.

Brown, L.P. 1995. *Pulse Check: National Trends in Drug Abuse—Fall*. Washington, D.C.: Office of National Drug Control Policy.

Calderone, L.; Grimes, P. & Shalev, M. 1986. Acute reversible cataract induced by xylazine and by ketamine-xylazine anesthesia in rats and mice. *Experimental Eye Research* 42: 331-37.

Carpenter, W.T. 1999. The schizophrenia ketamine challenge study debate. *Biological Psychiatry* 46: 1081-91.

Cloud, J. 1997. Is your kid on K? *Time* October 20: 56-57 [USA and Pacific editions only, but posted on World Wide Web].

Connell, P.H. 1958. *Amphetamine Psychosis*. Institute of Psychiatry Maudsley Monographs 5. : O.U.P.

Corbett D. 1990. Ketamine blocks the plasticity associated with prefrontal cortex self-stimulation. *Pharmacology, Biochemistry and Behaviour* 37 (4): 685-88.

Cosmopolitan. 1997. Sedate rape. *Cosmopolitan 25th Anniversary Issue*. March: 109.

Cotman, C.W.; Monaghan, D. & Ganong, A. 1988. Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. *Annual Review of Neuroscience* 11: 61-80.

Coyle, J.T. 1997. The nagging question of the function of N-acetylaspartylglutamate. *Neurobiology of Disease* 4 (3-4): 231-38.

Crysell, A. 1998. Lost in the K-hole. *Muzik* September: 45-8. (contact: muzik@ipc.co.uk).

Curran V. & Morgan, C. 2000. Cognitive, dissociative and psychogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction* 95: 575-90.

Dalgarno, P.J. & Shewan, D. 1996. Illicit use of ketamine in Scotland. *Journal of Psychoactive Drugs* 28 (2): 191-99.

Dershwitz, M.; Sreter, F.A. & Ryan, J.F. 1989. Ketamine does not trigger malignant hyperthermia in susceptible swine. *Anesthesia and Analgesia* 69 (4): 501-03.

Dixon, J.F.; Los, G.V. & Hokin, L.E. 1994. Lithium stimulates glutamate "release" and inositol 1,4,5-trisphosphate accumulation via activation of the N-methyl-D-aspartate receptor in monkey and mouse cerebral cortex slices. *Proceedings of the National Academy of Sciences U S A.* 91(18): 8358-62.

Domino, E.F.; Chodoff, P. & Corssen, G. 1965. Pharmacologic effects of Cl-581, a new dissociative anesthetic, in man. *Clinical and Pharmacological Therapeutics* 6: 279-91.

Dotson, J.W.; Ackerman, D.L. & West, L.J. 1995. Ketamine abuse. *Journal of Drug Issues* 25: 751-57.

Dragunow, M.; Currie, R.W.; Faull, R.L.M.; Robertson, H.A. & Jansen, K.L.R. 1989. Immediate early genes, kindling and longterm potentiation. *Neuroscience and Biobehavioral Reviews* 13: 301-13.

Drejer, J. & Honore, T. 1987. Phencyclidine analogues inhibit NMDA-stimulated [3H]GABA release from cultured cortex neurons. *European Journal of Pharmacology* 143: 287-90.

Drug Enforcement Agency. 1997. Ketamine abuse increasing. at: www.usdoj.gov/dea/program/diverson/divpub/substanc/ketamine.htm

Durieux, M.E. & Nietgen, G.W. 1997. Synergistic inhibition of muscarinic signalling by ketamine stereoisomers and the preservative benzthonium chloride. *Anesthesiology* 86 (6): 1326-33.

Ebert, B.; Mikkelson, S.; Thorkildsen, C. & Borgbjerg, F.M. 1997. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *European Journal of Pharmacology* 333: 99-104.

Ellison, G. 1995. The N-methyl-D-aspartate antagonists phencyclidine, ketamine and dizocilpine as both behavioral and anatomical models of the dementias. *Brain Research Reviews* 20: 250-67.

Engelhardt, W. 1997. Recovery and psychomimetic reactions following S- (+)-ketamine. *Anesthetist* 46 (Supplement 1):S38-S42.

Evans, W.S. 1998. Ontogenesis of auditory perception and memory at 20 weeks' gestation. Abstracts of the 1998 Annual Conference of the British Psychological Society, Brighton, p8.

Farber, P. 1995. *Futureritual : Magick for the 21st Century*. Chicago, Illinois: Eschaton Productions.

Farber, N.B.; Foster, J.; Duhan, N.L. & Olney, J.W. 1996. Olanzapine and fluperlapine mimic clozapine in preventing MK-801 neurotoxicity. *Schizophrenia Research* 21(1):33-37.

Farber, N.B.; Hanslick, J.; Kirby, C.; McWilliams, L. & Olney, J.W. 1998. Serotonergic agents that activate 5HT2A receptors prevent NMDA antagonist neurotoxicity. *Neuropsychopharmacology* 18 (1): 57-62.

Feinberg, I. & March, J.D. 1995. Observations on delta homeostasis, the one-stimulus model of NREM-REM alternation and the neurobiologic implications of experimental dream studies. *Behavioral Brain Research* 69 (1-2): 97-108.

Feldman, Z.; Gurevitch, B.; Artru, A.; Oppenheim, A.; Shohami, E.; Reichenthal, E. & Shapira, Y. 1996. Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. *Journal of Neurosurgery* 85(1):131-37.

Felser, J.M. & Orban, D.J. 1982. Dystonic reaction after ketamine abuse. *Annals of Emergency Medicine* 11: 673-74.

Fine, J. & Finestone, E.C. 1973. Sensory disturbances following ketamine anaesthesia: Recurrent hallucinations. *Anesthesia and Analgesia* 53: 428.

Food and Drug Administration. 1979. Ketamine abuse. *FDA Drug Bulletin* 9: 24.

Ghoneim, M.M.; Hinrichs, J.V.; Mewaldt, S.P. & Peterson, R.C. 1985. Ketamine: Behavioral effects of subanaesthetic doses. *Journal of Clinical Psychopharmacology* 5: 70-77.

Gibson, W. 1984. *Neuromancer*. London: Victor Gollancz.

Gill, J.R. & Stajic, M. 2000. Ketamine in non-hospital and hospital deaths in New York City. *Journal of Forensic Science* 45: 655-8.

Grant, I.S.; Nimmo, W.S. & Clements, J.A. 1981. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *British Journal of Anaesthesia* 53: 805-09.

Green, S.M.; Rothrock, S.G.; Lynch, E.L.; Ho, M.;Harris, T.; Hestdalen, R.; Hopkins, G.A.; Garrett, W. & Westcott, K. 1998. Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile in 1,022 cases. *Annals of Emergency Medicine* 31(6):688-97.

Grinspoon, L. & Bakalar, S.B. 1979. *Psychedelic Drugs Reconsidered*. New York: Basic Books/Harper Colophon.

Grof, S. 1988. *The Adventure of Self-Discovery—Dimensions of Consciousness and New Perspectives in Psychotherapy and Inner Exploration*. New York: State University of New York (SUNY) Press.

Hall, C.H. & Cassidy, J. 1992. Young drug users adopt "bad trip" anaesthetic. *The Independent* 2 April 2: 5.

Hansen, G.; Jensen, S.B.; Chandreash, L. & Hilden, T. 1988. The psychotropic effect of ketamine. *Journal of Psychoactive Drugs* 20 (4): 419-25.

Hefez, A. & Lanyi, G. 1972. Neuropsychiatric manifestations of ketamine hydrochloride. *Israel Annals of Psychiatry and Related Disciplines* 10: 180-87.

Hejja, P. & Galloon, S. 1975. A consideration of ketamine dreams. *Canadian Anaesthesia Society Journal* 22: 100-05.

Hirota, K. & Lambert, D.G. 1996. Ketamine: Its mechanism of action and unusual clinical uses. *British Journal of Anaesthesia* 77 (4): 441-44.

Hope, B.T. 1998. Cocaine and the ATP-1 transcription factor. *Annals of the New York Academy of Sciences* 844: 1-6.

Humphries, Y; Melson, M. & Gore D. 1997. Superiority of oral ketamine as an analgesic and sedative for wound care procedures in the pediatric patient with burns. *Journal of Burn Care Rehabilitation* 18 (1 Pt 1):34-36.

Hurt, P.H. & Ritchie, E.C. 1994. A case of ketamine dependence (Letter). *American Journal of Psychiatry* 151: 779.

Hustveit, O.; Maurset, A. & Oye, I. 1995. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacology and Toxicology* 77 (6): 355-59.

Irifune, M.; Shimzu, T. & Nomoto, M. 1991. Ketamine-induced hyperlocomotion associated with alteration of pre-synaptic components of dopamine neurons in the nucleus accumbens of mice. *Pharmacology, Biochemistry and Behavior* 40: 399-407.

Ishihara, H. 1997. Uneventful total intravenous anaesthesia with ketamine for schizophrenic surgical patients. *European Journal of Anaesthesiology* 14 (1):47-51.

Jansen, K.L.R. In press. *Ketamine, Dreams and Realities*. Saratoga, Florida: Multidisciplinary Association for Psychedelic Studies (contact : carla@maps.org).

Jansen, K.L.R. 1997a. The ketamine model of the near -death experience: a central role for the NMDA receptor. *Journal of Near-Death Studies* 16 (1): 5-27.

Jansen, K.L.R. 1997b. Adverse psychological effects associated with the use of ecstasy (MDMA) and their treatment. In: N. Saunders (Ed.) *Ecstasy Reconsidered*. London: Neal's Yard Desk Top Publishing Studio.

Jansen, K.L.R. 1997c. The brain drain. *The Face* 3 (3): 166-70.

Jansen, K.L.R. 1996a. Neuroscience, ketamine and the near-death experience: The role of glutamate and the NMDA receptor. In: L.J. Bailey. & J. Yates (Eds.) *The Near-Death Experience: A Reader*. New York: Routledge.

Jansen, K.L.R. 1996b. Using ketamine to induce the near-death experience: Mechanism of action and therapeutic potential. In: C. Ratsch & J.R. Baker (Eds.) *Yearbook for Ethnomedicine and the Study of Consciousness* [Jahrbuch furr Ethnomedizin und Bewubtseinsforschung] Issue 4, 1995; Berlin: VWB 55-81.

Jansen, K.L.R 1993. Non-medical use of ketamine. *British Medical Journal* 306: 601-02.

Jansen, K.L.R. 1990a. Neuroscience and the near-death experience: Roles for the NMDA-PCP receptor, the sigma receptor and the endopsychosins. *Medical Hypotheses* 31: 25-29.

Jansen, K.L.R. 1990b Ketamine: Can chronic use impair memory? *International Journal of Addictions* 25: 133 -9.

Jansen, K.L.R 1989. Near-death experience and the NMDA receptor. *British Medical Journal* 298: 1708-9.

Jansen, K.L.R.; Faull, R. & Dragunow, M. 1989. Excitatory amino acid receptors in the human cerebral cortex: A quantitative autoradiographic study comparing the distribution of [^{3}H]TCP, [^{3}H]glycine, 1-[^{3}H]glutamate, [^{3}H]AMPA and [^{3}H]kainic acid binding sites. *Neuroscience* 32: 587-607.

Johnstone, R.E. 1973. A ketamine trip. *Anesthesiology* 39: 460.

Kamaya, H. & Krishna, P.R. 1987. Ketamine addiction (letter). *Anaesthesia* 67 (5): 861-62.

Ketcham, D.W. 1990. Where there is no anaesthesiologist: The many uses of ketamine. *Tropical Doctor*. 20 (4): 163-66.

Klausen, N.O.; Wiberg-Jorgensen, F. & Chraemmer-Jorgensen, B. 1983. Psychotomimetic reactions after low-dose ketamine infusion. *British Journal of Anaesthesia* 55 (4): 297-301.

Krumholz, W.; Demel, C.; Jung, S.; Meuthen, G.; Knecht, J. & Hempelmann, G. 1995. The effects of thiopentone, etomidate, ketamine and midazolam on several bactericidal functions of polymorphonuclear leucocytes in vitro. *European Journal of Anaesthesiology* 12 (2): 141-46.

Krupitsky, E.M. & Grinenko, A.Y. 1997. Ketamine psychedelic therapy (KPT): A review of the results of ten years of research. *Journal of Psychoactive Drugs* 29 (2): 165-83. [Reprints: Research Laboratory, Leningrad Regional Dispensary of Narcology, 19/1 Novo-Deviatkino, Vsevolozhsky District, St. Petersburg 188661, Russia 26; e-mail: kru@lond.spb.su].

Krystal , J.H.; Karper, L.P.; Bennett, A.; D'Souza, D.C.; Abi-Dargham, A; Morrissey, K; Abi-Saab, D.; Bremner, J.D.; Bowers, M.B.; Suckow, R.F.; Stetson, P., Heninger, G.R. & Charney, D.S. 1998. Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. *Psychopharmacology (Berlin)* 135(3):213-29.

Krystal, J.H.; Karper, L.P.; Seibyl, J.P.; Freeman, G.K.; Delaney, R.; Bremner. J.D.; Heniger, G.R.; Bowers, M.B. & Charney, D.S. 1994. Subanesthetic effects of the noncompetitive antagonist ketamine in humans. *Archives of General Psychiatry* 51: 199-214.

Kugler, J. & Doenicke, A. 1994. Ketamine-anticonvulsive and proconvulsive actions. *Anaesthesist* 43 (Suppl 2): S2-S7.

Kumar, A.; Kumar, A; Bajaj, A.; Sarkar P. & Grover, V.K. 1992. The effect of music on ketamine induced emergence phenomena. *Anaesthesia* 47 (5): 438-39.

Lahti, A.C.; Koffel, B.; LaPorte, D. & Tamminga, C.A. 1995. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 13 (1): 9-19.

Leary, T. & Sirius, R.U. 1997. *Design for Dying*. London: Thorsons/ HarperCollins.

Licata, M.; Pierini, G. & Popoli, G. 1994. A fatal ketamine poisoning. *Journal of Forensic Science* 39 (5): 1314-20.

Lilly, J.C. 1978. *The Scientist: A Novel Autobiography*. New York. Bantam Books/J. B. Lippincott. [now available from Ronin Publishing]

Lindefors, N.; Barati, S. & O'Connor, W.T. 1997. Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. *Brain Research* 759 (2): 205-12.

Malhotra, A.K.; Breier, A.; Goldman, D.; Picken, L. & Pickar, D. 1998. The apolipoprotein E epsilon 4 allele is associated with blunting of ketamine-induced psychosis in schizophrenia. A preliminary report. *Neuropsychopharmacology* 19 (5): 445-8.

Malhotra, A.K.; Pinals, D.A.; Adler, C.M.; Elman, I.; Clifton, A.; Pickar, D. & Breier, A. 1997. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology* 17(3): 141-50.

Malhotra, A.K.; Pinals, D.A.; Weingartner, H.; Sirocco, K.; Missar, C.D.; Pickar, D. & Breier, A. 1996. NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14 (5): 301-07.

Malinovsky, J.M.; Servin,F.; Cozian, A.; Lepage, J.Y. & Pinaud, M. 1996. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *British Journal of Anaesthesiology* 77 (2): 203-07.

Malinovsky, J.M.; Lepage, J.Y.; Cozian A; Mussini, J.M.; Pinaudt, M & Souron, R. 1993. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 78 (1): 109-15.

Miranda, A.F.; Boegman, R.J.; Beninger, R.J. & Jhamandas, K. 1997. Protection against quinolinic acid-mediated excitotoxicity in nigrostriatal dopaminergic neurons by endogenous kynurenic acid. *Neuroscience* 78 (4): 967-75.

Modvig, K.M. & Nielsen S.F. 1977. Psychological changes in children after anaesthesia: A comparison between halothane and ketamine. *Acta Anaesthesiology Scandinavica* 21(6): 541-44.

Moghaddam, B. 1994. Recent basic findings in support of excitatory amino acid hypotheses of schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry* 18 (5): 859-70.

Moghaddam, B.; Adams, B.; Verma, A. & Daly, D. 1997. Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *Journal of Neuroscience* 7 (8): 2921-27.

Moore, M. & Alltounian, H. 1978. *Journeys Into The Bright World*. Massachusetts: Para Research.

Moore, N.N. & Bostwick, J.M. 1999. Ketamine dependence in anesthesia providers. *Psychosomatics* 40 (4): 356-59.

Morita, T.; Hitomi, S.; Saito, S.; Fujita, T.; Uchihashi, Y. & Kuribara, H. 1995. Repeated ketamine administration produces up-regulation of muscarinic acetylcholine receptors in the forebrain, and reduces behavioral sensitivity to scopolamine in mice. *Psychopharmacology (Berlin)* 117(4): 396-402.

Nakao, S.; Adachi, T.; Murakawa, M.; Shinomura, T.; Kurata, J.; Shichino, T.; Shibata, M.; Tocyama, I.; Kimura, H. & Mori, K. 1996. Halothane and diazepam inhibit ketamine-induced c-Fos expression in the rat cingulate cortex. *Anesthesiology* 85 (4): 874-82.

Nakao, S.; Arai, T.; Mori, K.; Yasuhara, O.; Tooyama, I. & Kimura, H. 1993. High-dose ketamine does not induce c-Fos protein expression in rat hippocampus. *Neuroscience Letters* 151(1): 33-36.

Nishimura, M. & Sato, K. 1999. Ketamine stereoselectively inhibits rat dopamine transporter. *Neuroscience Letters* 274: 131-4.

Nishina, K.; Akamatsu, H.; Mikawa, K; Shiga, M; Maekawa, N.; Obara, H. & Niwa, Y. 1998. The inhibitory effects of thiopental, midazolam, and ketamine on human neutrophil functions. *Anesthesia and Analgesia* 86 (1): 159-65.

Olney, J.W. 1994. Neurotoxicity of NMDA receptor antagonists: An overview. *Psychopharmacology Bulletin* 30 (4): 533-40.

Olney, J.W., Labruyere, J., & Price, M.T. 1989. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 244: 1360-62.

Olney, J.W.; Labruyere, J.; Wang, G.; Wozniak, D.F.; Price, M.T. & Sesma, M.A. 1991. NMDA antagonist neurotoxicity: Mechanism and prevention. *Science* 254: 1515-18.

Oyama, T.; Matsumoto, F. & Kudo, T. 1970. Effects of ketamine on adrenocortical function in man. *Anesthesia and Analgesia* 49: 697-700.

Parke-Davis. 2000. *Product Information Sheet: Ketalar. ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1999-2000.* London: Datapharm Publications Ltd.

Perel, A. & Davidson, J.T. 1976. Recurrent hallucinations following ketamine. *Anaesthesia* 31: 1081-83.

Pfeiffer A.; Brantl, V.; Herz, A. & Hemrich, H.M. 1986. Psychotomimesis mediated by k receptors. *Science* 233: 744-76.

Plourde, G., Baribeau, J. & Bonhomme, V. 1997. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. *British Journal of Anaesthesia* 78 (5): 524-29.

Poole, R. & Brabbins, C. 1996. Drug induced psychosis. *British Journal of Psychiatry* 168: 135-38.

Reier, C.E. 1971. Ketamine—"dissociative agent" or hallucinogen? *New England Journal of Medicine* 284 (14): 791-2.

Release. 1997. *Release Drugs and Dance Survey: An Insight into the Culture.* London: Release. [contact: Release, 388 Old Street, London EC1V 9LT, U.K.]

Reuter. 1996. Party craze for cat's drug. *Guardian* July 2: 11.

Rogo, D.S. 1984. Ketamine and the near-death experience. *Anabiosis: The Journal of Near-Death Studies* 4: 87-96.

Rothman, S.M, & Olney, J.W. 1987. Excitotoxicity & the NMDA receptor. *Trends in Neurosciences* 10: 299-302.

Rozza, A.; Masoero, E.; Favalli, L.; Lanza, E.; Govoni, S.; Rizzo, V. & Montalbetti, L. 2000. Influence of different anaesthetics on extracellular amino acids in rat brain. *Journal of Neuroscience Methods* 101: 165-69.

Sabom, M.B. 1982. *Recollections of Death: A Medical Investigation.* New York: Harper and Row.

Schorn, T.O.F. & Whitwam, J.G. 1980. Are there long term effects of ketamine on the nervous system? *British Journal of Anesthesia* 52: 967-68.

Schwender, D.; Daunderer, M.; Kunze-Kronawitter, H.; Klasing, S.; Poppel, E. & Peter, K. 1997. Awareness during general anaesthesia—incidence, clinical relevance and monitoring. *Acta Anaesthesiology Scandinavica* 11: 313-14.

Sharp, F.R 1998. Personal communication.

Sharp, F.R.; Butman, M.; Aardalen, K.; Nickolenko, J.; Nakki, R.; Massa, S.M.; Swanson, R.A. & Sagar, S.M. 1994. Neuronal injury produced by NMDA antagonists can be detected using heat shock proteins and can be blocked with antipsychotics. *Psychopharmacology. Bulletin* 30(4): 555-60.

Shelton, G. & Sheridan, D. 1975. L.A. breakdown. *Freak Brothers 4.* San Francisco: Ripoff Press.

Siegel, R.K. 1978. Phencyclidine and ketamine intoxication: A study of recreational users. In: R.C. Peterson & R.C. Stillman (Eds.) *Phencyclidine Abuse: An Appraisal.* NIDA Research Monograph No. 21. Rockville, Maryland: National Institute on Drug Abuse.

Sklar, G.S.; Zukin, S.R. & Reilley, T.A. 1981. Adverse reactions to ketamine anesthesia. Abolition by a psychological technique. *Anaesthesia* 36: 183-90.

Skovmand, K. 1996. Swedes alarmed at ketamine misuse. *Lancet* 348 (9020): 122.

Slaby, A. 1994. *Handbook of Psychiatric Emergencies.* Fourth Ed. Bridgeport, Connecticut: Appleton and Lange.

Smith, J.A. & Santer, L.J. 1993. Respiratory arrest following intramuscular ketamine injection in a 4-year old child. *Annals of Emergency Medicine* 22: 613-15.

Sobel, R.M.; Morgan, B.W. & Murphy, M. 1999. Ketamine in the ED: Medical politics versus patient care. *American Journal of Emergency Medicine* 17 (7): 722-25.

Soyka, M.; Krupitski, G. & Volki, G. 1993. Phenomenology of ketamine induced psychosis. *Sucht* 5: L327-31.

Stafford, P. 1992. *Psychedelics Encyclopaedia.* 3rd Ed. Berkeley, California: Ronin Publishing.

Strassman, R.J. 1984. Adverse reactions to psychedelic drugs: A review of the literature. *Journal of Nervous and Mental Disease* 172: 477-595.

Sybert, J.W. & Kyff, J.V. 1983. Ketamine treatment of status epilepticus. *Anesthesiology* 58: 203.

Taylor, P.A. & Towey, R.M. 1971. Depression of laryngeal reflexes during ketamine anesthesia. *British Medical Journal* ii: 688-9.

Thompson, G.E. 1972. Ketamine-induced convulsions. *Anesthesiology* 37: 662-63.

Thomson, A.M.; West, D.C. & Lodge, D. 1985. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: A site of action of ketamine? *Nature* 313: 479-81.

Tomlinson, A. 1994. Ketamine. *World Anaesthesia OnLine.* Issue 4: Article 5. at: http://www.hda.ox.ac.uk/wfsa/html/u04/u04-01010.htm

Topp, L.; Hando, J.; Degenhardt, L.; Dillon, P.; Roche, A. & Solowij, N. 1998. *Ecstasy Use in Australia.* Monograph No. 39. Sydney, Australia: National Drug and Alcohol Research Centre.

Turner, D.M. 1994. *The Essential Guide to Psychedelics.* California: Panther Press [out of print, but may be found at: http://www.geocities.com/HotSprings/Spa/4558/]

Van der Kolk, B.A. 1997. The psychobiology of posttraumatic stress disorder. *Journal of Clinical Psychiatry* 58 (Suppl. 9): 16-24.

Verma, A. & Moghaddam, B. 1996. NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: Modulation by dopamine. *Journal of Neuroscience* 16: 373-79.

Vollenweider, F.X.; Leenders, K.L.; Oye, I.; Hell, D. & Angst, J. 1997a. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *European Neuropsychopharmacology* 7: 25-38.

Vollenweider, F.X.; Leenders, K.L.; Scharfetter, C.; Antonini, A.; Maguire, P.; Missimer, J. & Angst, J. 1997b. Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG). *European Neuropsychopharmacology* 7:9-24.

Weil, A. & Rosen, W. 1983. *Chocolate to Morphine: Understanding the Mind-Active Drugs.* Boston, Massachusetts: Houghton-Mifflin.

Weiner, A.L; Vieira, L., McKay, C.A. & Bayer, M.J. 2000. Ketamine abusers presenting to the emergency department: A case series. *Journal of Emergency Medicine* 18 (4): 447-51.

Weiss, J. 1986. Ketamine protects cultured neocortical neurons from hypoxic injury. *Brain Research* 380: 186-90.

White, M.J. & Ryan, C. 1996. Pharmacological properties of ketamine. *Drug and Alcohol Review* 15: 145-55.

Williams, K.; Dichter, M.A. & Molinoff, P.B. 1992. Up-regulation of N-methyl-D-aspartate receptors on cultured cortical neurons after exposure to antagonists. *Molecular Pharmacology* 42: 147-51.

Winnicott, D.W. 1958. *Collected Papers.* New York: Basic Books.

World Health Organisation. 1992. *The ICD-10 Classification of Mental and Behavioural Disorders.* Geneva: World Health Organisation.

Young, L.A.; Young, L.G.;Klein, M.M.; Klein, D.M. & Beyer, D. 1977. *Recreational Drugs.* New York: Collier Books.

Zielmann, S. & Grote, R. 1995. The effects of long-term sedation on intestinal function. *Anaesthesist* 44 (Suppl 3): S549-S558.

Zsigmond, E.K. 1976. Arterial hypoxemia caused by i.v. ketamine. *Anesthesia and Analgesia* 55: 311-14.

Zsigmond, E.K. 1971. Malignant hyperthermia with subsequent uneventful anesthesia. *Anesthesia and Analgesia* 50: 1111-12.