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Meant to be an authoritative guide for psychiatrists and others interested in understanding and applying ketamine psychedelic psychotherapy (KPP), this paper focuses on its pharmacology, phenomenology, and clinical applications. Ketamine is a dissociative anesthetic widely used by physicians and veterinarians in the United States. In addition to its anesthetic and dissociative properties, ketamine also has a multitude of other psychological and pharmacological properties, which include analgesic, sedative, neuroprotective, anxiolytic, antidepressant, stimulant, euphoriant, and hallucinogenic effects. The literature on the clinical application of KPP is comprehensively reviewed, practical advice for using KPP is given, and the pharmacology and phenomenology of ketamine-induced psychedelic experiences are explored, including in relationship to transpersonal healing and possible iatrogenic consequences of misuse of KPP.

Keywords: *psychedelic, ketamine, psychotherapy, transpersonal, consciousness*

Ketamine is an extremely interesting substance, especially from a transpersonal healing perspective, as it not only has a wide range of potential clinical applications, including through what is here called ketamine psychedelic psychotherapy (KPP), but it is the only legally-available (i.e., through a physician's off-label prescription without having to go through regulatory hurdles) substance within the United States that can reliably produce psychedelic experiences. Consequently, we review the literature on the clinical application of KPP, and focus on the phenomenology of ketamine-induced psychedelic experiences in terms of possible clinical applications within a transpersonal context.

Arylcyclohexylamines: Ketamine's Family Tree

The arylcyclohexylamines (also known as arylcyclohexamines or arylcyclohexanamines) were originally developed as anesthetics by Parke-Davis. Unlike all other anesthetic agents, except perhaps nitrous oxide, the arylcyclohexylamines do not generally extinguish consciousness, but instead appear to "dissociate" mind from body (thus the name of "dissociative anesthetics"). The arylcyclohexylamines predominantly block the N-methyl-D-aspartate (NMDA) receptor, a target for the neurotransmitter glutamate in the brain, and prevent the NMDA receptor from being activated by glutamate (Ahmadi & Mahmoudi, 2005; Ahmadi, Khalili,

Hajikhani, & Naserbakht, 2011). In addition to NMDA antagonism, the arylcyclohexylamines produce μ opioid receptor agonism (Itzhak & Simon, 1984) and cause dopamine reuptake inhibition (Chaudieu et al., 1989). Some of the arylcyclohexylamines also produce sigma receptor agonistic (He et al., 1993), nACh receptor antagonistic (Eterović et al., 1999), and D_2 receptor agonistic (Seeman, Ko, & Tallerico, 2005) actions.

Antagonism of the NMDA receptor generates dissociative (hallucinogenic), anesthetic, neuroprotective and anticonvulsant effects; stimulation of the sigma and D_2 receptors contributes to hallucinogenic (psychomimetic) effects; activation of the μ-opioid receptor causes analgesic and anxiolytic effects; blockade of the dopamine transporter mediates stimulant and euphoriant effects (as well as adding to psychomimetic effects in higher doses); the combination of the two last qualities confers a strong antidepressant effect; and the combination of all the above pharmacological properties make the arylcyclohexylamines powerful psychedelic drugs.

The first member of the arylcyclohexylamine class to be discovered was phencyclidine. It was synthesized in 1926, eventually patented in 1953 by the Parke-Davis pharmaceutical company for use as an anesthetic agent for humans and animals, and was marketed under the brand name Sernyl® (referring to serenity). By 1965, its use with humans was discontinued as clinical studies revealed that patients experienced what was then seen as "psychotic" symptoms when emerging from the drug's effects (so-called "emergence delirium"). Today, it is rarely used even in the veterinary community. However, it continues to be legally available for research purposes in the United States, but as a Schedule II controlled substance.

Phencyclidine re-emerged as a drug of abuse in the mid-1960s due to its strong euphoriant and psychedelic qualities. The drug was relatively easy and inexpensive to manufacture in clandestine laboratories and it quickly became popular on the streets, with names such as "Angel Dust" and PCP. PCP can be pressed into pills or put in capsules and swallowed. When ingested orally, effects are felt in 30 to 45 minutes and last from 6 to 24 hours. Doses of less than 5 mg produce euphoriant effects (feelings of elation and joy, relaxation, feelings of unreality and mild dissociation from the environment), while doses of 10 mg or more produce psychedelic effects (distorted sense of one's body, a feeling of weightlessness, distorted sense of time and space, visual and auditory hallucinations).

PCP use spread in the 1970s. When PCP is snorted or smoked (for example, users dipped tobacco or cannabis cigarettes in the liquid form of PCP or sprinkled its powder form on a leafy material like tobacco or cannabis), the effects are felt within 4 to 5 minutes and last from 4 to 6 hours. PCP can also be injected, although this appears to be a less common route of administration.

PCP use may have peaked around 1978, when *People* magazine called it the country's "number one" drug problem. PCP became infamous for its recurrent binges (so-called "runs"), when chronic users would take PCP repeatedly for 2 to 3 consecutive days at a time without eating or sleeping. It was estimated that at least 7 million Americans used PCP on at least one occasion between 1975 and 1983. The American Psychiatric Association (APA) Diagnostic and Statistical Manual (DSM)-IV-TR (APA, 2000) devoted a separate chapter to this substance entitled Phencyclidine-Related Disorder. By the mid-1980s, PCP use began declining, perhaps partly as a result of the increased popularity of ketamine and crack cocaine. Eventually, PCP use slowly faded away, although there is still some manufacture by clandestine chemists. Today PCP is classified as a hallucinogen and the new APA (2013) DSM-5 places its effects in the Hallucinogen-Related Disorder category, with classical hallucinogens.

The second compound from the arylcyclohexylamines class, eticyclidine, was also developed by Parke-Davis and evaluated for anesthetic potential under the code name CI-400. Eticlydine is very similar in effects to phencyclidine and is slightly more potent. Parke-Davis did not continue its research of eticyclidine after the development of ketamine, a similar drug with more favorable properties. Nevertheless, eticyclidine (under the name of PCE) did make its way to the streets and was briefly abused in the 1970s and 1980s. It did not become popular with recreational users due to its unpleasant taste and tendency to cause nausea. Eticyclidine was placed into the U.S. Schedule I list of illegal drugs in the 1970s and its use is unknown today.

Ketamine was the third compound from the class of arylcyclohexylamines that Parke-Davis developed as part of an effort to find a safer and more predictable anesthetic agent than its precursors. Unlike the first two creations of Parke-Davis, ketamine proved to be

the most promising compound and eventually became the company's most successful anesthetic, sedative, analgesic, anxiolytic, and neuroprotective agent.

Ketamine Pharmacology

Ketamine hydrochloride, a phencyclidine derivative, was originally invented in 1962 by the American organic chemist Calvin Stevens, who initially called the compound CI-581 and later renamed it ketamine. Ketamine, like all the arylcyclohexylamines, predominantly targets the neurotransmitter glutamate, which is an excitatory messenger that turns on the brain cells and triggers an electrical impulse. Ketamine opposes this action by blocking the N-methyl-D-aspartate (NMDA) receptor. It prevents the NMDA receptor from being activated by glutamate (Anish, Berry, Burton, & Lodge, 1983; Thomson, West, & Lodge, 1985). Ketamine also has direct and/or indirect effects on the μ opioid (Fink & Nagai, 1982; Fidecka, 1987; Freya, Latish, Schmidhammer, & Portoghese, 1994; Herman, Vocci, & Bridge, 1995; Latasch & Freye, 1993; Smith et al., 1980; Winters et al., 1988), dopamine (French, Mura, & Wang, 1993; Irifune, Shimizu, & Nomoto, 1991; Irifune et al., 1997; Keita, Lecharny, Henzel, Desmonts, & Mantz, 1996; Nishimura & Sato, 1999; Rao, Kim, Lehmann, Martin, & Wood, 1990), serotonin (Kim, Park, & Park, 1998; Lindefors et al., 1997; Martin, 1982; Minami, Minami, & Harris, 1997; Pallotta, Segieth, & Whitton, 1998), acetylcholine (Cohen, Chan, & Trevor, 1973; Durieux & Nietgen, 1997; Mimura et al., 1992; Morita et al., 1995; Toro-Matos, Rendon-Platas, Avila-Valdez, & Villarreal-Guzman, 1980), GABA (Drejer & Honore, 1987; Lindefors et al., 1997), cannabinoid (Richardson, Aanonsen, & Hargreaves, 1998; Stella, Schweitzer, & Piomelli, 1997), nitric oxide (Abajian, Page, & Morgan, 1973; Carroll, Lac, Asencio, & Kragh, 1990; Galley & Webster, 1996; Lin, Chiou, & Wang, 1996) and sigma (Hustveit, Maurset, & Oye, 1995) systems.

Ketamine hydrochloride may be administered via a variety of routes including oral, sublingual, rectal, intranasal, intramuscular, and intravenous routes. Ketamine is a highly lipid soluble chemical and, as a result, its clinical effects present within 45 to 50 seconds of administration when given intravenously, within 3 to 4 minutes when given intramuscularly, within 5 to 10 minutes when given intranasally, and within 20 to 30 minutes when given orally (Alonso-Serra & Wesley, 2003). The 1992 version of the Physicians' Desk Reference (PDR) indicated that ketamine use is usually devoid of life-threatening side-effects and that several instances of unintentional administration of overdoses of ketamine of up to ten times that usually required for surgical anesthesia have been followed by prolonged but complete recovery (PDR Network, 1992).

More than 10,000 published reports describe ketamine's high level of effectiveness and its confirmed biological safety in most cases, although like all drugs there is the possibility of some adverse effects in some people (Bauman, Kish, Baumann, & Politis, 1999; Dachs & Innes, 1997; Ersek, 2004; Reich & Silvay, 1989; Ross & Fochtman, 1995; Shapiro, Wyte, & Harris, 1972). Clinical studies have generally detected no long-term impairment of behavior or personality functioning as a result of repeated ketamine use (Siegal, 1978), but some individual case studies of ketamine dependence have raised questions at times (e.g., Jansen 1990, 2000, summary in Jansen 2001) and there have been some recent concerns about, for example, toxicity to the urinary system (e.g., Selby et al., 2008; Wood, 2013.)

According to several in vitro and animal studies, ketamine can even have neuroprotective properties under some circumstances (Hoffman et al., 1992; Shapira, Artru, & Lam, 1992; Shapira, Lam, Eng, Laohaprasit, & Michel, 1994). Subsequently, ketamine has been used as a neuroprotective agent to prevent brain damage from head trauma, strokes, heart attacks, epileptic seizures, low oxygen levels, and low blood-sugar levels (Albanese et al., 1997; Bar-Joseph, Guilburd, Tamir, & Guilburd, 2009; Filanovsky, Miller, & Kao, 2010; Hirota & Lambert, 1996; Hughes, 2011; Mayberg, Lam, Matta, Domino, & Winn, 1995; Rothman et al., 1987; Shapira et al., 1994; Weiss, Goldberg, & Choi, 1986).

Ketamine Biochemistry and Electrophysiology

Extensive research of the biochemical aspects of ketamine has been done by one of us, a Russian researcher, Evgeny Krupitsky, and a U.S. researcher, John Krystal, who both have conducted extensive independent studies since the 1980s. Krupitsky and Krystal later collaborated in researching the biochemistry of ketamine (Krupitsky et al., 2001; Krystal et al., 2003a).

Krupitsky conducted ketamine studies at the Center for Research in Addiction and Psychopharmacology in St. Petersburg, Russia, researching the effects of ketamine administration on metabolism of biogenic amines, including dopamine, serotonin, monoamine oxidase type A (MAO-A), monoamine oxidase type B

(MAO-B), GABA, ceruloplasmin, and B-endorphin. The results of these biochemical investigations show that during the ketamine session, dopamine levels were increased, serotonin and GABA concentrations were not altered significantly, ceruloplasmin activity and the B-endorphin levels were increased, and the activity of MAO-A in blood serum and MAO-B in blood platelets significantly decreased. The results provided biochemical data showing that the pharmacological actions of ketamine affect monoaminergic and opioidergic neurotransmitter metabolism (Krupitsky et al., 1990).

These changes in the metabolism of neurotransmitters allow some opinions to be formed about the underlying neurochemical mechanisms of ketamine's psychedelic action. For example, an increase of ceruloplasmin activity causes a corresponding increase in the conversion of monoamines into adrenochromes, which have hallucinogenic activity (Anokhina, 1975; Nalbandyan, 1986). This particularly takes place under the conditions of inhibited MAO activity and increased dopamine levels. This is of interest because such conditions are typical for the action of many classical hallucinogens (Hamox, 1984; McKenna, Towers, & Abbott, 1984). The fact that the pharmacological actions of ketamine affected both monoaminergic and opioidergic systems, two neurochemical systems involved in pathogenesis of alcoholism, is an important result of this biochemical investigation, as it is possible that these actions contribute to the efficacy of KPP.

Krupitsky has also used EEG computer-assisted data in studying underlying mechanisms of KPP (Krupitsky & Grinenko, 1997). EEG recordings were taken before, during, and after the ketamine session by placing 16 electrodes according to the international scheme. After analog-digital conversion, standard programs of computer assisted spectral EEG analysis and topographic mapping of EEG were employed. The data of EEG computer-assisted analysis demonstrated that ketamine increases delta activity (1.5 – 2X) and particularly theta-activity (3 – 4X) in all regions of the cerebral cortex. This is evidence of limbic system activation during ketamine sessions, as well as evidence of the reinforcement of the limbic cortex interaction (Pribram, 1971). These findings can also be considered to a certain extent as indirect evidence of the strengthening of the interactions between the so-called conscious and unconscious levels of the mind during KPP (Simonov, 1987).

There are also some data indicating that the interaction between the frontal cortex and the limbic system are important for the action of ketamine on the brain. Previously, it has been demonstrated in positron emission tomography (PET) with fluorodeoxyglucose (FDG) studies that ketamine-induced disturbances of glutamatergic neurotransmission results in a specific hyperfrontal metabolic pattern in the human brain associated with psychedelic experiences, specifically visionary experience and ego-dissolution (Vollenweider et al., 1994). Also, frontal lobotomy reduces the psychedelic response to phencyclidine in schizophrenic patients (Itil, Keskiner, Kiremitci, & Holden, 1967). Ketamine activates the interaction between brain structures associated with cognitive processing of information (frontal cortex) and structures involved in the processes of emotions, motivations, memory, and subconscious experiences and perceptions (limbic structures). Such enhanced interaction may be an important neurophysiological mechanism underlying the phenomenology of ketamine psychedelic experiences and the dramatic psychological changes caused by those experiences.

John Krystal, chair of the department of psychiatry at Yale University School of Medicine, directed ketamine research at the Connecticut Mental Health Center in New Haven. He utilized ketamine primarily as a psychomimetic agent to study the neurobiology of schizophrenia, and focused on ketamine's effects on perceptual and cognitive functioning (Krystal et al., 1994, 1998a, 1998b, 1999, 2000). Krystal's group also collected a substantial body of evidence demonstrating that ketamine's major underlying mechanism of action on the brain is the blockade of the N-methyl-D-asparate (NMDA) receptors, which are mostly located in the cortex and hippocampus and are involved in processes of integration and transmission into the cortex of incoming signals from all sensory modalities (Krystal et al., 1994). This finding was confirmed by another group of investigators (Oye, Paulsen, & Maurset, 1992), verifying that a significant reduction of sensory transmission and activation of autonomous cortex-limbic interactions may be important underlying mechanisms of the psychedelic action of ketamine.

In addition, Krystal's group completed clinical research studying the effect of ketamine's NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients (Krystal et al., 1998b).

Twenty male patients with alcoholism who had not consumed alcohol for 10 days to 4 weeks prior to the study completed 3 test days that involved the administration of very low (0.1 mg/kg) and low-to-medium (0.5 mg/kg) doses of ketamine or saline solution under randomized double-blind conditions. Ethanol-like subjective effects were assessed using visual analog scales to measure "high" and degree of similarity to ethanol, cocaine, and cannabis, and also employed a scale assessing the number of standard alcohol drinks producing similar subjective effects. This team concluded that ketamine produced ethanol-like effects in a dose-related way on each scale, exhibiting similarity to ethanol. However, its effects were judged more similar to the sedative, rather than stimulant, alcohol effects. Ketamine effects also were more like ethanol than cannabis or cocaine. Ethanol-like effects were more prominent at the higher ketamine dose, a dose rated as similar to greater levels of ethanol intoxication. The production of ethanol-like subjective effects by ketamine supports the potential clinical importance of NMDA receptor antagonism among the mechanisms underlying the subjective effects of ethanol in humans (Krystal et al., 1998b; Krystal et al., 2003b).

Ketamine Development

In 1964, ketamine was officially tested on the first human subjects, the inmates at the Jackson Prison in the State of Michigan. The study was done by Edward Domino, MD, an American clinical pharmacologist (Domino, Chodoff, & Corssen, 1965). Domino was the first investigator to discover that ketamine has multiple pharmacological effects, including anesthetic, analgesic, and antidepressant effects.

Domino was also the first researcher who discovered the "schizophrenomimetic" (hallucinogenic) properties of ketamine. He reported that most of his subjects described strange experiences like feeling "spaced out" and "floating" (Domino, 2010). Initially, Domino used the word "dreaming" to describe the drug's hallucinogenic effect. However, the Parke-Davis scientists did not like that name out of the company's concerns that the U.S. Food and Drug Administration (FDA) may label ketamine as "psychotomimetic," which might stop the clinical development of a very promising pharmaceutical. Domino discussed the unusual actions of ketamine with his wife and mentioned that the subjects were "disconnected" from their environment. His wife came up with the term "dissociative anesthetic" that "dissociates" so-called mind from body (Domino, 2010). From that time, the "dissociative anesthetic" name has been assigned not only to ketamine hydrochloride, but also to the entire class of psychoactive arylcyclohexylamines.

In 1966, Parke-Davis patented ketamine under the brand name Ketalar for use as an anesthetic in humans and animals. Ketamine was successfully tried on American soldiers in the Vietnam War (when it got nicknamed the "buddy drug" because it could be administered by a corpsman or a fellow soldier due to its relative safety and ease of administration). In the course of the Vietnam War, it became the most widely used battlefield anesthetic, sedative, and analgesic, giving an excellent opportunity for American anesthesiologists and surgeons to become familiar with the agent.

Ketamine rapidly became the drug of the choice used by the U.S. military for CASEVAC, a military term for the emergency patient evacuation of casualties from a combat zone to a clearing station or a nearby hospital, increasingly by helicopter in the jungle wars. In most cases a wounded soldier would be in a hospital receiving medical care within 35 minutes of being wounded. Patients were moved directly from the battlefield directly into the preoperative and resuscitation shelter while under the effects of field-administered ketamine.

Impressively, the use of ketamine as an agent for analgesia and conscious sedation during battlefield-casualty evacuations helped to decrease the mortality rate of wounded soldiers who made it to medical treatment from 4.5% during the Korean War to 2.6% during the Vietnam War. The U.S. soldiers knew that, if they were wounded, they had a better chance of surviving and quickly receiving medical care than in any other war in which the United States had previously participated, a fact that did much to boost troop morale (Vietnam Studies, Department of the Army, 1973).

Eventually, in 1970, the FDA approved the use of ketamine anesthesia with children, adults, and the elderly. Since that time, ketamine has been widely used in hospitals and for office procedures due to its rapid onset, short duration of action, and superior safety. Ketamine has now been in clinical practice for 50 years and has been continually used as a usually very safe anesthetic to evoke general anesthesia, a first line agent to induce procedural conscious sedation, a potent non-opiate analgesic to control both acute and chronic pain, a unique neuroprotective agent to prevent brain damage, a superior anxiolytic to control preoperative and end-of-life anxiety,

a rapid-onset antidepressant to treat chronic depression and other treatment-resistant psychiatric conditions, and, for a period, the only legal hallucinogenic drug available to conduct psychedelic psychotherapy (although there has been some forward movement in that regard in recent years, with some work recommencing using substances such as psilocybin and DMT; Friedman, 2006).

Unsurprisingly, ketamine has also become popular on "the streets" for its strong euphoriant effects and potent hallucinogenic properties. There are some matters of relevance to therapeutic issues to be learned from its non-medical and "recreational" use, so this paper also reviews some of that material.

Ketamine Pharmacotherapy

It has been proposed (Haas & Harper, 1992; White, Way, & Trevor, 1982) that the "ideal" agent for anesthesia must possess the following specific characteristics:

- Effective in inducing anesthesia
- Minimal cardiovascular effects
- Minimal respiratory effects
- Ability to titrate
- Rapid onset of action
- Predictable duration of effect
- Short elimination half-life
- Anxiolytic at sub-anesthetic doses
- Analgesic in sub-anesthetic doses
- Soluble in water
- Stable in solution
- Absence of pain on injection
- Absence of post-injection irritation.

A few classes of drugs, such as the opioids, barbiturates, and benzodiazepines, meet some, but not all, of these criteria. Today, ketamine is one of only a very few agents that regularly meets all of these criteria of an ideal anesthetic, when the dose is suitable for the patient and purpose. Certainly a large bolus dose of ketamine as a sudden intravenous push can affect respiration and intracranial pressure, but in that instance it can often be argued that the dose was not suitable for the patient and purpose. Ketamine is included in the 18th edition of the World Health Organization (2013) model list of essential medicines, promulgating its availability in a health system.

It has been a half a century since Domino administered ketamine to the first human subjects (Domino et al., 1965). Since then, ketamine has become widely accepted as an outstanding agent to reduce preoperative anxiety and facilitate induction of general anesthesia, as it appears to have virtually all of the desired properties of the ideal agent. Subsequently, ketamine has been used worldwide for an extensive range of various procedures, including preoperative sedation, intraoperative anesthesia, and postoperative analgesia (Haas & Harper, 1992).

While there are many anesthetic drugs available, internationally ketamine remains amongst the most popular general anesthetics, especially in the Developing World and emergency contexts, because of its low cost, ease of storage, advantageous airway and respiratory properties, hemodynamic stability, broad range of clinical applications, and excellent therapeutic index (Craven, 2007; USAARL Report, 2010). Ketamine's wide-therapeutic window (Green, Clem, & Rothrock, 1996; Green et al., 1999; Strayer & Nelson, 2008) makes it the anesthetic of choice in austere or resource-poor environments where monitoring equipment may be rudimentary or absent and a single operator must provide the anesthetic and monitor a patient (Green et al., 1996; Strayer & Nelson, 2008). It can be administered via almost any route, although intravenous (IV) and intramuscular (IM) administrations are by far the most popular and best studied for surgical anesthesia (Mistry & Nahata, 2005). The initial dose of ketamine administered intravenously ranges from 1 mg/kg – 4.5 mg/kg, and intramuscular doses range from 6.5 – 13 mg/kg (White et al., 1982). Ketamine is highly lipid soluble and, as such, clinical effects present within one minute of administration when given intravenously and within five minutes when given intramuscularly (Alonso-Serra & Wesley, 2003).

Today, the most frequent use of ketamine has been for conscious sedation for physically or emotionally painful procedures (procedural sedation) and analgesia for acute and chronic pain, both on the battlefield and in emergency departments worldwide, and also in vetinary medicine. For use in sedation only, the doses of ketamine are 0.5 – 0.75 mg/kg IV or 2 – 4 mg/kg IM; for use as an analgesic and/or anxiolytic agent, the doses of ketamine are 0.2 – 0.3 mg/kg IV, 0.5 – 1.5 mg/kg IM and intranasal, and 1 – 2 mg/kg sublingual, oral and rectal.

Peak plasma concentrations have been reported to occur within 1 min following IV administration, 5 to 15 minutes following IM injection, 30 minutes after oral administration and 45 minutes after rectal administration (Domino et al., 1984; Grant, Nimmo,

& Clements, 1981; Pedraz et al., 1989). Elimination is primarily by the kidney, and only a small percentage is recovered in the urine as the unchanged drug (Chang, Savory, & Albin, 1970). The elimination half-life of ketamine is approximately 2 hours (Domino et al., 1984), although there are some longer estimates. Metabolites which are also active NMDA receptor blockers can sometimes be detected in urine for up to a week or more (e.g., Ebert, Mikkelsen, Thorkildsen, & Borgbjerg, 1997.)

When ketamine is administered in small (analgesic, anxiolytic, and sedative) doses, it does not usually impair spontaneous respirations and does not increase blood pressure and heart rate (Subramaniam, Subramaniam, & Steinbrook., 2004; Visser & Schug, 2006; White et al., 1982), which makes ketamine an especially desirable analgesic/anxiolytic/sedative for use on the battlefield and in evacuation procedures. Today, combat medics continue using ketamine for battlefield sedation and pain management because of its minimal impact on medic carrying capacity and ability to withstand environmental extremes. It is also much more field expedient than any other analgesic due to its low occurrence of side effects (Guldner, Petinaux, Clemens, Foster, & Antoine, 2006). In a recent review of analgesic options for pain relief on the battlefield, Black and McManus (2009) wrote that, in sub-anesthetic doses, ketamine is almost ideal as an analgesic due to providing profound-pain relief, potentiating opioids, preventing opioid hyperalgesia, and its margin of safety.

The use of ketamine by emergency physicians prior to the 1990s was infrequent (Green & Krauss, 2004a, 2004b). However, after a landmark study by Green and Johnson (1990), it has become one of the most popular agents for procedural sedation and analgesia in emergency departments. In their review of 11,589 administrations of ketamine for sedation, Green and Johnson (1990) firmly established the drug's safety and efficacy for medical use.

Since then, ketamine has been extensively used as an analgesic in intensive and acute care medicine (particularly in emergency medicine), and there has been considerable further research on the efficacy, safety, contraindications, guidelines, and dosing of ketamine (Green & Krauss, 2004a, 2004b; Lin & Durieux, 2005; Mistry & Nahata, 2005). It has been well documented that ketamine has a very low frequency of adverse effects in doses used for conscious sedation and analgesia (Alonso-Serra & Wesley, 2003; Cherry, Plummer, Gourlay, Coates, & Odgers, 1995; Howes, 2004; Jennings, Cameron, & Bernard, 2011; Porter, 2004). Today ketamine is routinely stocked in all emergency departments across the United States, Australia, New Zealand, and many other countries (Sacchetti, Senula, Strickland, & Dubin, 2007); due to its exceptional analgesic and sedative properties at low doses, ketamine has been widely used for treatment of acute postoperative pain, so-called breakthrough pain in patients with acute and/or chronic pain, and for management of neuropathic pain disorder, ischaemic limb pain disorder, refractory cancer pain, and as a pediatric sedation tool for use with acutely injured children (Bell, Dahl, Moore, & Kalso, 2006; Buvanendran & Kroin, 2009; Carr et al., 2004; Ellis, Husain, Saetta, & Walker, 2004; Green & Krauss., 2004a, 2004b; Howes, 2004; McGlone, Howes, & Joshi, 2004; Petrack, Marx, & Wright, 1996; Rakhee & Milap, 2005; Schmid Sandler, & Katz, 1999; Visser & Schug, 2006). In addition, low-dose ketamine has successfully served as an effective adjunct to standard opioid therapy, as well as an adjunct to various non-opiate analgesic agents (Schmid, Sandler, & Katz, 1999).

One of the reasons ketamine has been repeatedly studied and scrutinized is its uniqueness among all other sedatives, hypnotics, and analgesics (primarily opiates, barbiturates, and benzodiazepines). The standard definition of conscious procedural sedation is dose-dependent alterations in consciousness that result in mild to deep sedation, preserving responsiveness to verbal or tactile stimuli. Ketamine, in contrast, exerts its effect through a functional and electrophysiological dissociation or disconnect between the thalamo-neocortical and limbic areas of the brain (Green & Krauss, 2004a, 2004b; Krupitsky & Grinenko, 1997; Mistry & Nahata, 2005). Therefore, it does not have a characteristic dose-response continuum by progressive titration; the dissociation is present or absent with a very narrow transition zone (Mistry & Nahata, 2005). At doses below a certain threshold, ketamine produces analgesia and anxiolysis; however, once the critical dosage threshold of roughly 1 – 1.5 mg/kg IM (or 0.5 – 0.75 mg/kg IV) is reached, the characteristic dissociative state abruptly appears (Krauss & Green, 2006). Furthermore, dissociation is described as a "trance-like cataleptic state" of "sensory isolation" (Mistry & Nahata, 2005), meaning little or no responsiveness is present.

Most importantly, unlike other traditional sedatives, ketamine usually preserves cardiovascular

stability, spontaneous respirations and protective airway reflexes, even when exerting its full effect (Green & Krauss, 2004a, 2004b; Mistry & Nahata, 2005). Because of this, the dissociative state is not consistent with the definitions of conscious sedation (Green & Krauss, 2004a, 2004b; Krauss & Green, 2000, 2006), which has resulted in a separate definition for ketamine procedural sedation, namely "dissociative sedation" (American College of Emergency Physicians, 2005). It should be noted that ketamine is a nonreversible agent; once the dissociative state is initiated, it cannot be aborted (Alonso-Serra & Wesley, 2003; White et al., 1982).

Ketamine performs as a superior fast-acting analgesic and anxiolytic in low doses (0.2 – 0.3 mg/kg IV, 0.5 – 1 mg/kg IM and intranasal, and 1 – 2 mg/kg sublingual and oral), as an effective reliable sedative in medium doses (0.5 – 0.75 mg/kg IV, 1.5 – 4 mg/kg IM), and a safe short-acting anesthetic in high doses (1 – 4.5 mg/kg IV and 6.5 – 13 mg/kg IM).

Ketamine-Induced Emergence Phenomena

Although ketamine is biologically safe in most instances of medical use and has an excellent safety profile, it is not without controversy, as it generates peculiar psychological side-effects (vivid imagery, visual hallucinations, excitement, irrational behavior) dubbed "emergence delirium," it has a high dependence potential when abused, and use in a drug-abuse context has recently resulted in multiple reports of harm to the kidney and bladder (cystitis) in some people (e.g., Bokor & Anderson 2014; Meng et al., 2013; Selby et al., 2008; Tam et al., 2014; Wood, 2013). This has become a fairly hot topic in, for example, Hong Kong urology, where ketamine abuse is rife, but appears not to have been specifically reported by long-term heavy users of medically-sourced ketamine such as John Lilly, and those who contributed to one of our author's (Jansen, 2001) book, *Ketamine: Dreams And Realities*. However, some of the latter did complain of mysterious "K pains" in the pelvic region, and it seems increasingly likely that these persons may have been susceptible to these urological issues as the evidence continues to mount, from multiple medical specialists in multiple countries, that some long-term heavy users are susceptible to urological side-effects. There have also now been animal studies pointing to a mechanism (e.g., Gu et al., 2014), so this is unlikely to be one of those random panics that have characterised the War on Drugs (e.g., scare tactics, such as "LSD damages your chromososmes") that were later discredited as propaganda (Dishotsky, Loughman, Mogar, & Lipscomb, 1971.)

Domino was the first clinician who documented that 30% of patients had an "emergence delirium" after ketamine anesthesia (Domino et al., 1965). Subsequently, he asked Parke-Davis to contact Elliot Luby, a psychiatrist at the Lafayette Clinic, who had previously used phencyclidine (Sernyl) to induce the same phenomena in normal volunteers and psychiatric patients (Domino, 2010). The Parke-Davis researchers were concerned that Luby would conclude that ketamine was schizophrenomimetic, which would perhaps result in the Parke-Davis executives and lawyers stopping its development. It was a reasonable concern, as Luby earlier documented that phencyclidine-induced states had similarity to "schizophrenic syndrome" (Luby, Cohen, Rosenbaum, Gottlieb, & Kelley, 1959). Consequently, Parke-Davis insisted that their own psychiatrist observed the subjects recovering from ketamine anesthesia. This psychiatrist concluded the subjects had an emergence reaction quite similar to diethyl ether (Domino, 2010).

Emergence delirium is not a new phenomenon in clinical practice. Eckenhoff and colleagues (1961) had reported the signs of "hyperexcitation" in patients "emerging" from diethyl ether, phencyclidine, or cyclopropane anesthesia. This phenomenon refers to a clinical condition in which patients experience a variety of "behavioral disturbances," including crying, disorientation, sobbing, and thrashing during early emergence from anesthesia (Eckenhoff et al., 1961). Emergence delirium (a.k.a. "emergence reaction," "emergence agitation" and "emergence excitation") is defined as the disturbance of a patient's attention to and awareness of the environment accompanied by disorientation, hyperactive motor behavior, and perceptual alterations immediate postanesthesia (Sikich & Lerman, 2004).

Parke-Davis understandably selected the less frightening name of "emergence phenomenon" rather than "delirium," and seems to have underreported the frequency of this controversial side-effect. For many years, Parke-Davis reported on their ketamine (Ketalar) data sheet that the frequency of emergence phenomena was only 12%. This number was too low, however, and was eventually dropped from their later data sheet (Parke-Davis Product Information Sheet, 1999-2000). The actual percentage reporting emergence phenomena after ketamine anesthesia

is close to 40% in many studies (Abajian et al., 1973; Hervey & Hustead, 1972; Khorramzadeh & Lofty, 1973; Krestow, 1974; O'Neil, Winnie, Zadigian, & Collins, 1972; Overton, 1975; Sadove, Shulman, & Fevgold, 1971). One study even reported a 100% incidence range of emergence phenomenon (Garfield, Garfield, Stone, Hopkins, & Johns, 1972).

It was quickly discovered that "emergence phenomena" may occur independently of anesthesia and can be reliably generated by an administration of a sub-anesthetic dose of ketamine. Collier reported that, at one-sixth to one-tenth of the dose used for general anesthesia, ketamine can create psychedelic experiences with disconnection from surroundings, perception of floating, becoming disembodied as a mind or soul, and even dying and going to a different world (Collier, 1972). He also noted that loss of reality contact appears more pronounced than with other psychedelics. In addition, Collier reported that dissociative experiences often seemed so authentic that users were not sure whether they had or had not actually become "disembodied."

The discovery that ketamine is a powerful psychedelic drug did not end its popularity as an outstanding anesthetic agent. Instead, use of benzodiazepines (the most frequently used are midazolam, lorazepam, and diazepam) and increasingly propofol have been utilized to control emergence problems due to their strong amnestic and dream-suppressing properties. In addition, the combined use of ketamine and benzodiazepines or propofol has the advantage of providing increased sedation and anxiolysis (Cartwright & Pingel, 1984; Domino et al., 1984; Dundee, 1990; Haas & Harper, 1992; Tobin, 1982; Toft & Romer, 1987; White et al., 1982; White et al., 1988).

Ketamine as a Psychedelic Drug

The ketamine dissociative experience (emergence phenomena) is, in fact, a non-ordinary state of consciousness (NOSC) during which the individual's awareness and perception are dramatically changed and radically refocused. This psychedelic experience is often induced by intramuscular injections of ketamine in doses that are typically used for dissociative sedation and lasts from 45 minutes to one hour. The patient completely loses contact with external reality and gets involved in a profound psychedelic experience. The ketamine-induced non-ordinary states of consciousness may include (Collier, 1972; Jansen, 1989a, 1989b, 1997; Khorramzadeh & Lofty, 1976; Kolp et al., 2006, 2007; Krupitsky et al., 1992; Krupitsky & Grinenko, 1996, 1997; Krupitsky & Kolp, 2007; Lilly, 1968; Moore & Alltounian, 1978; Weil & Rosen, 1983):

- Feelings of leaving one's body (i.e., out-of-body experience)
- Awareness of becoming a non-physical being
- Emotionally intense visions (e.g., of deceased relatives, "angels," "spirits")
- Encounters with archetypal beings (e.g., Christ, Buddha, Krishna)
- Encounters with non-terrestrial beings (e.g., "space aliens")
- Visits to mythological realms of consciousness
- Re-experiencing the birth process
- Vivid dreams and memories of past or future incarnations
- Experience of psychological death and rebirth of self (i.e., near-death experience)
- Feelings of ego dissolution and loss of identity
- Experience of reliving one's life
- Deep feelings of peace and joy
- Sense of transcending normal time and space
- Feelings of interconnectedness with all people and nature
- Feelings of cosmic unity with the Universe and God
- Sense of sacredness
- Profound sense of ineffability of the experience
- Intuitive belief that the experience is a source of objective truth about the nature of "absolute reality."

John Lilly, an American neuroscientist, psychiatrist, and "psychonaut" (explorer of his own mind, often with the aid of substances), began a series of self-experiments with psychedelic substances in the early 1960s. Initially, he used LSD, which he sometimes self-administered in a sensory isolation flotation tank (Lilly, 1972). Circa 1971, Lilly started an exploration of the use of ketamine by self-administering various doses of ketamine via intramuscular injections, often using an isolation tank to enhance its effects (Lilly, 1978).

Lilly documented a relationship between dosage levels and the qualities of ketamine experiences that he himself had. He reported that intramuscular injections of ketamine at 25 mg did not cause visual images, whereas over 30 mg it produced such images when eyes are closed. At above 50 mg, visual images

became stronger; however, in his case there was no dissociation of the mind from the body. At above 75 mg, visual images significantly increased and feelings of detachment of the mind from the body began. At above 100 mg, visual images became intense even when the eyes were open, and feelings of complete dissociation of the mind from the body were common. At above 150 mg, the mind completely disconnected from the body and feelings of total dissolution of ego were common. The doses above 300 mg produced unconsciousness (Lilly, 1978). However, like many long-term ketamine users, Lilly developed a notable tolerance to ketamine over the years, and thus his own dose-response relationships changed (summarized in Jansen, 2001). Lilly proposed utilizing ketamine as a psychotherapeutic agent by using ketamine-induced non-ordinary states of consciousness for reprogramming the interface of brain-mind, and also described ketamine's antidepressant effects (Lilly, 1972).

Ketamine-Induced Non-Ordinary States of Consciousness

Ketamine induces at least four distinct NOSCs that depend on at least three major factors (as is the case with all other classical hallucinogenic substances): the dose of ketamine, the physical "setting" of the ketamine administration, and the mindset (often just referred to as "set") of the person prior to the ketamine administration (see Table 1). These different states of consciousness may be partly distinguished by: a) the degree of a dissociation of the mind from the body, and b) the degree of ego dissolution.

In considering the effects of substances on a person, amongst other factors it is necessary to consider the dose taken, how it is taken, and the speed at which it is taken, the size and gender of the person, other substances taken (either before, at the same time or afterwards), the tolerance of the individual, and the set and setting. The term set includes personality, past experiences, mental health, mood, motivations, intelligence, imagination, attitudes, what is going on in his or her life, and his or her expectations. The term setting refers to the conditions of use, including the physical, social, and emotional environment, including the other people present.

The first state is an empathogenic (or "generating a state of empathy" or "heart-opening") experience. The term "empathogenic" was proposed in the early 1980s by Ralph Metzner, and is generated in response to an injection of a low sub-psychedelic dose of ketamine,

Table 1. Ketamine-induced non-ordinary states of consciousness

State	Features	Typical Ketamine Dose	Duration
Empathogenic Experience	Awareness of body; comfort and relaxation; reduced ego defenses; empathy, compassion, and warmth; love and peace; euphoria; mind is dreamy with non-specific colorful visual effects	Low sub-psychedelic dose similar to that used for anxiolysis and/or analgesia (0.25 mg/kg – 0.5 mg/kg IM, or 25 – 50 mg IM)	45-60 mins
Out-of-Body Experience (OBE)	Complete separation from one's body; significantly diminished ego defenses; visits to mythological realms of consciousness; encounters with non-terrestial beings; emotionally intense visions (e.g., deceased relatives, spirits); vivid dreams of past and future incarnations; re-experiencing the birth process	Medium psychedelic dose such as that used for mild conscious dissociative sedation (0.75 mg/kg – 1.5 mg/kg IM, or 75 mg – 125 mg IM)	45-60 mins
Near-Death Experience (NDE)	Departure from one's body; complete ego dissolution/loss of identity; experienced physical (body) and psychological (mind) death; experience being a single point of consciousness simply aware of itself; reliving one's life; aware of how actions have affected others, with moral judgment of self	High psychedelic dose such as that used for moderate to severe conscious dissociative sedation (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 250 mg IM)	45-60 mins
Ego-Dissolving Transcendental Experience (EDT)	Ecstatic state of the dissolution of boundaries between the self and external reality; complete dissolution of one's body and self (soul); transcending normal mass/time/space continuum; collective consciousness; unity with Nature/Universe; sacredness	Rare in low doses (0.25 mg/kg – 0.5 mg/kg IM, or 25 – 50 mg IM), more common in high psychedelic doses (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 200 mg IM)	45-60 mins

the type of dose that may be used for anxiolysis and/or analgesia (0.25 mg/kg – 0.5 mg/kg IM, or 25 mg – 50 mg IM). This state lasts from 45-50 minutes to 1-2 hours and may be characterized by the following features:

- The awareness of the body remains well-preserved
- The body feels very comfortable and relaxed
- The ego functioning is well-maintained;however, the ego defenses are significantly lessened
- The person experiences feelings of empathy and compassion for themselves
- The mind feels emotional warmth, well-being, and joy
- Strong feelings of love and peace are prevailing
- Feelings of euphoria, pleasure and joy are common
- Feelings of ecstasy and enhanced sensuality are frequent
- The mind is dreamy with frequent non-specific colorful visual effects
- The person may feel they have forgiveness and understanding of themselves and for those with whom they have important relationships.

It is also entirely possible for these doses to produce marked dysphoria and other unpleasant changes in mental and physical state. This is far more likely to happen if the set and setting are negative.

The empathogenic NOSC is like the state induced by sub-psychedelic doses of classical hallucinogenic substances (LSD, psilocybin, DMT, mescaline, etc.), or regular doses of classical empathogenic substances (MDA, MDMA, 2-CB, etc.). This state can be combined with guided imagery or verbalized meditations and may sometimes be utilized to resolve long-standing intra-psychic conflicts, to treat the aftereffects of trauma in the victims of physical and sexual abuse or other assault, to control the symptoms of post-traumatic stress disorder (e.g., in soldiers), or to resolve interpersonal problems in spousal and family relationships. Unlike the other three NOSC, which are more intense and overpowering, an empathogenic experience is more likely to leave the patient with an ability to consciously recall this particular non-ordinary state of consciousness.

The second NOSC is an "out-of-body experience" (OBE), and may be induced in response to an injection of a medium psychedelic dose of ketamine, which is in the range used for mild conscious dissociative sedation (0.75 mg/kg – 1.5 mg/kg IM, or 75 mg – 125 mg IM). This state lasts from 45 minutes to 1 hour and may be characterized by the following features:

- Feelings of complete separation from one's body
- The ego defenses are significantly diminished; however, the rudimentary ego structure is still preserved and the experiencer is well-aware of the self
- Awareness of becoming a non-corporeal being
- Apparent visits to mythological realms of consciousness
- Apparent encounters with non-terrestrial beings (e.g., "space aliens")
- Emotionally intense visions (e.g., deceased relatives, "angels," "spirits")
- Encounters with archetypal beings (e.g., Krishna, Buddha, Christ)
- Vivid dreams and memories of past or future incarnations
- Re-experiencing the birth process.

This NOSC is similar to the state that can sometimes be induced by medium doses of classical hallucinogenic substances (LSD, psilocybin, mescaline, etc.), although the visions are more realistic, well-defined, and frequently get organized into a specific "story." This type of experience can bring to the conscious awareness a plethora of unconscious material and may be utilized as an adjunct to psychodynamic psychotherapy. This state may sometimes be enhanced when combined with calm, evocative music (e.g., classical, Trance, or New Age) to assist with relaxation and immersion into the experience. Unlike an empathogenic experience, OBE leaves the person with only a partial ability to consciously recall all details of this particular NOSC after the experience, partly due to an avalanche of phantasmagoric visions and sensory overload, and partly for physical reasons as more extensive NMDA receptor blockade interferes with memory formation (Collingridge, 1987; Jansen, 1990a, 1990b).

The third NOSC is a "near-death experience" (NDE), which may be induced by an injection of a high psychedelic dose of ketamine, in the range that may be used for moderate to severe conscious dissociative sedation (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 250 mg IM). This state lasts from 45 minutes to 1 hour and is characterized by the following features:

- Feelings of complete departure from one's body
- Feelings of complete ego dissolution and loss of identity
- A strong belief of being physically dead
- Experience of psychological death of the mind (the self)
- Feelings of becoming a single point of consciousness (the Self, or a soul) that is simply aware of itself with no other points of reference
- Sensations of moving through a tunnel
- Experience of reliving one's entire life
- Becoming aware that one is responsible for every thought, word, and action of one's life prior to the NDE
- Awareness of how others were affected by one's thoughts, words, and actions
- Performing the moral judgment of the self based on one's own sense of right and wrong holding one accountable for one's thoughts, words, and actions
- Experience of visiting non-physical realities (either paradisiacal or hellish realms of consciousness) based on one's own self-judgment
- Encounters with non-corporeal entities
- Experience of visiting an eternal, featureless void (nothingness)
- Experience of psychological rebirth of the ego.

This NOSC is similar to the state that is sometimes induced by high doses of classical hallucinogenic substances (e.g., LSD, psilocybin, DMT, mescaline), although the visions may be more intense, well-structured, and liable to become organized into a form of life review. Some research has found that approximately 70% of NDEs are accompanied by feelings of calm and peace, while about 30% of NDEs are very frightening (Greyson, 1983; Greyson & Stevenson, 1980). This NOSC type of experience can sometimes bring enhanced insight into one's deeds and misdeeds, and may sometimes be very beneficial as an adjunct to existential psychotherapy as well as to so-called "ego death/rebirth" psychotherapy (Krupitsky & Grinenko, 1997; Kungurtsev, 1991). This state may also be combined with non-associative, evocative music to assist with an immersion into the experience. Similar to the OBE, the NDE leaves the patient with only a partial ability to consciously recall this particular NOSC on the following day, although key features of the overall experience may be surprisingly well-remembered (i.e., surprising because ketamine's action at NMDA receptors and on neurotransmitters is likely to impede short-term memory.)

Ketamine's ability to replicate NDEs is well-documented (Collier, 1972; Domino, Chodoff, & Corssen, 1965; Ghoneim, Hinrichs, Mewaldt, & Petersen, 1985; Grinspoon & Bakalar, 1979; Kungurtsev, 1991; Lilly, 1968; Rumpf et al., 1969; Siegel, 1978, 1980, 1981; Sputz, 1989; Stafford & Golightly, 1967; White et al., 1982). One of our authors (Jansen) analyzed similarities between ketamine-induced transpersonal experiences and NDEs in a series of studies, concluding that 150-200 mg of ketamine can reproduce all of the features commonly associated with NDEs (Jansen, 1989a, 1989b, 1990a, 1990b, 1991, 1997, 2001). Three of this paper's authors (Jansen, Kolp, & Sylvester) had personal NDEs from natural causes, as well as NDE-like ketamine-induced experiences, and can personally verify the striking similarities between both phenomena (e.g., a compelling sense of being dead, sensations of moving through a tunnel, one's life review, visits of non-physical realities, encounters with non-corporeal entities, an experience of the void).

NDEs can be very transformative in some people, and can induce positive changes in spiritual development and worldview (Ring, 1980, 1984; Ring & Valeriano, 1998). Ketamine-induced NDEs appear to be equivalent to natural NDEs and may facilitate stable recovery by accelerating patients' psycho-spiritual growth and broadening their worldviews (Kolp et al., 2007, 2009; Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007). In addition to bringing an insight into one's existential problems, the NDE can also generate a spontaneous resolution of the patient's addictive illnesses, psychological problems, and personality disorders. These experiences can also generate a spontaneous spiritual conversion and a dramatic improvement in moral character (Kolp et al., 2007, 2009; Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

The fourth type of NOSC is perhaps the most fascinating and sometimes the most potentially beneficial ketamine-induced experience, as it is an ego-dissolving transcendental (EDT) experience (an ecstatic state of the dissolution of boundaries between the self

and external reality) which may be characterized by the following features:

- Feelings of complete dissolution of one's body
- Feelings of complete dissolution not only of ego but also the self
- Sense of transcending normal mass/space/time continuum
- Feelings of interconnectedness with all people (or sense of experiencing collective consciousness)
- Feelings of cosmic unity with nature
- Feelings of cosmic unity with the universe
- Feelings of becoming a "Unified Field"
- Feelings of becoming God, frequently experienced as an ocean of brilliant white light
- Deep feelings of love, peace, serenity, joy, and bliss
- Profound sense of sacredness of the experience
- Profound sense of ineffability of the experience
- Intuitive belief that the transcendental experience is a source of objective truth about the nature of absolute reality.

There are some indications that the EDT experience is not always dose dependent and may occur even with a low dose of ketamine (0.25 mg/kg – 0.5 mg/kg IM, or 25 – 50 mg IM), although it is more frequent with a high psychedelic dose of ketamine (2.0 mg/kg – 3.0 mg/kg IM, or 150 – 250 mg IM). The EDT experience may last from 45 minutes to 1 hour and may be an excellent adjunct to transpersonal psychotherapy.

Similar to the NDE, the EDT experiences sometimes generate some resolution of the patient's addictive illnesses, psychological problems, and personality disorders, including instances of spontaneous healing from chronic psychosomatic illnesses, particularly where these are dissociative/conversion in type. In addition, there are some anecdotal accounts of patients who had a spontaneous remission of some forms of serious medical disease (Fenwick & Fenwick, 1995; Grey, 1985; Morse & Perry, 1992; Ring & Valeriano, 1998; Roud, 1990). Like NDEs, EDT experiences have the advantages of potentially rapidly accelerating patients' psychospiritual growth, broadening their worldviews, and possibly generating a spontaneous spiritual change with an improvement in moral character (Kolp et al., 2007, 2009; Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

Psychedelic Psychotherapy

The acute psychological effects of ketamine can be psychedelic in nature. There are many previous studies on the effectiveness of psychedelic psychotherapy (Grinspoon & Bakalar, 1979; Grof, 1980; Jansen, 1997, 2001; Khorramzadeh & Lofty, 1973, 1976; Kolp et al., 2006, 2007, 2009; Krupitsky & Kolp, 2007; Krupitsky et al., 1992, 1997, 2002; Kurland et al., 1971; Leary, Metzner, & Alpert, 1964; Roquet, 1974; Strassman, 1995) suggesting that incorporating a psychedelic experience into psychotherapy may have beneficial effects in many ways, including:

- Contributing to the cathartic process
- Stabilizing positive psychological changes
- Enhancing personal growth and self-awareness
- Catalyzing insights into existential problems
- Increasing creative activities
- Broadening spiritual horizons
- Harmonizing relationships with the world and other people.

Although the ceremonial and therapeutic uses of hallucinogenic drugs have been known worldwide for millennia (Furst, 1972; Schultes & Hofmann, 1979), scientific research of psychedelic-assisted psychotherapy began more recently. Some of the experiments of the great British chemist Sir Humphrey Davy, later President of the Royal Society, with nitrous oxide at the Pneumatic Institution at Bristol, in the late 18th and early 19th century, hinted at what was possible; unfortunately, the opportunity was entirely missed, including the opportunity to develop nitrous oxide as what would have been the first anesthetic, with Sir Davy later dismissing his experiments into the effects of nitrous oxide on the mind as frivolous. Consequently, surgical operations continued to cause terrible pain for at least another 100 years. The failure to see the opportunities was partly cultural and has been related to the 19th century cultural attitude to pain (Holmes, 2008). Cultural attitudes, rather than issues genuinely related to science and medicine, may currently play an important role in greatly restricting the use of psychedelic psychotherapy in contemporary society, but there are some signs of a thaw.

The Italian psychoanalyst Baroni (1931) started using a mixture of mescaline and Datura stramonium as an aid in psychoanalytical psychotherapy in the 1920s, and the work of Meduna (1950) with carbon dioxide

is also worthy of note. However, psychedelic research largely began in the 1950s, after Sandoz Laboratories distributed lysergic acid diethylamide (LSD) and psilocybin to all researchers interested in hallucinogen-assisted therapy. Since then, the scientific investigation into psychotherapeutic uses of psychedelic drugs has been conducted in many countries and resulted in the release of dozens of books and more than 1000 peer-reviewed clinical papers reporting the use of psychedelic substances administered to more than 40,000 subjects (Dyck, 2005; Grinspoon & Bakalar, 1979; Passie, 1997). Numerous clinical research studies of the subjects treated with psychedelic compounds, performed from the late 1950s through the present time, repeatedly demonstrated sometimes impressive treatment outcomes (e.g., Grob, 1998, 2002; Grof, 1980; Grinspoon & Bakalar, 1979; Kolp et al., 2006, 2007, 2009; Krupitsky & Kolp, 2007; Pahnke, 1968, 1969; Pahnke, Kurland, Goodman, & Richards, 1969; Pahnke, Kurland, Unger, Savage, & Grof, 1970; Pahnke, Kurland, Unger, Savage, Wolf, & Goodman, 1970; Pahnke, McCabe, Olsson, Unger, & Kurland, 1969; Richards, 1979/1980; Richards, Grof, Goodman, & Kurland, 1972; Richards et al., 1979; Richards, Rhead, DiLeo, Yensen, & Kurland, 1977; Walsh & Grob, 2005; Watts, 1973; Yensen & Dryer, 1993/1994).

Hallucinogen-assisted psychotherapy evolved into three major methodologies: hypnodelic psychotherapy, psycholytic ("mind-loosening") psychotherapy, and psychedelic ("mind-manifesting") psychotherapy. Hypnodelic psychotherapy has its goal as being to maximize the power of hypnotic suggestion by combining it with the low (sub-psychedelic) doses of hallucinogenic substances in order to lower ego defenses without actually creating a visionary experience (Grof, 1980). Hypnodelic psychotherapy goes back to the nineteenth century, when ether, nitrous oxide, and chloroform were used to induce and deepen hypnotic states (e.g., Schrenck-Notzing, 1891). Later on, a procedure called "narcoanalysis" was developed to use an amphetamine/barbiturate-induced state of excitation/sedation to recall repressed conflicts (Horsley, 1943). Its use in the treatment of "traumatic combat neuroses" (one of the former names for post-traumatic stress disorder) attained some importance (Grinker & Spiegel, 1945).

Psycholytic therapy (a.k.a "psycholysis") involves the use of medium doses of psychedelic drugs that create a powerful mind-altering experience without dissolution of ego functioning (Eisner, 1997; Eisner & Cohen, 1958; Leuner, 1967). This technique was regularly practiced in numerous European treatment centers during the 1950s and 1960s. In 1954 Sandison and Spencer reported "abreactive memory actualizations" leading to a remarkable progress of "neurotic" patients treated with LSD (Sandison & Spencer, 1954). Around the same time Leuner (1959) developed a day-dream technique in psychotherapy that became established through the present time as "guided affective imagery" (Leuner, 1977, 1984). He documented that treatment with low doses of hallucinogens predictably generated regression and catharsis experiences in his psychotherapy patients (Leuner, 1959, 1971, 1977, 1984).

The earlier investigators reported that psycholytic psychotherapy (or psycholysis) presented to psychotherapists unique opportunities to overcome rigid defense mechanisms in treatment-resistant patients (Arendsen, 1963; Leuner, 1971; Mascher, 1967). Other reported advantages of psycholysis, in addition to the amplification of psychotherapeutic process, were its capacity to increase the effectiveness of treatment and to shorten the length of psychotherapy to half of the typical time (Arendsen-Hein, 1963; Leuner, 1971, 1977, 1984; Mascher, 1967).

Psychedelic therapy involves the use of higher doses of hallucinogenic drugs, with the aim of inducing ego-dissolving transpersonal (e.g., transcendental, mystical, spiritual) peak experiences (Grinspoon & Bakalar, 1979; Grob, 1998, 2002; Grof, 1978, 1980, 1986; Grof & Halifax, 1976; Grof, Goodman, Richards, & Kurland, 1973; Pahnke, 1968; Pahnke et al., 1969, 1970; Richards et al., 1972, 1977, 1979; Walsh & Grob, 2005; Watts, 1973; Yensen & Dryer, 1993/1994). This method was initially developed by Hoffer and Osmond in the United States (Hoffer, 1967). In 1950, they observed that many alcoholic patients developed a spontaneous remission after the frightening experiences of a delirium tremens (Hoffer, 1967). Subsequently, they resolved to induce a facsimile of delirium tremens with high doses of LSD, in order to generate abstinence in alcoholic patients. To their surprise, those patients who had positive experiences, such as religious, spiritual, or mystical experiences, had even longer lasting therapeutic effects (Hoffer, 1967). Following their original experiments, Osmond and Hoffer developed the technique of psychedelic psychotherapy based on the induction of mystical

experiences. They used a quasi-religious preparation, high doses of LSD, specific surroundings, and evocative music to attempt to induce a transformative mystical state of consciousness (Hoffer, 1967).

Pahnke (1962) conducted a double-blind experiment and scientifically documented that the induction of mystical experiences ("Unio mystica") can generate rapid acceleration of psychospiritual growth. His work was further replicated by Leary, Litwin, and Metzner (1963) who came to the same conclusion.

The reports based on ethnographic observations of the ritual administration of certain hallucinogenic plants are also relevant. La Barre (1989) and Andritzky (1989) documented dramatic positive personality changes in individuals with alcoholism who participated in indigenous shamanic ceremonies (Peyote cult and Brazilian Ayahuasca religion).

During the 1960s and 1970s, the psychedelic technique was extensively studied and further optimized at the NIMH Psychiatric Research Center and Spring Grove Hospital (Grof, 1975, 1978; Pahnke et al., 1970; Richards et al., 1977; Yensen & Dryer, 1993/1994). Both hypnodelic and psycholytic psychotherapies were usually conducted repeatedly at intervals of 1-4 weeks, between 10 and 50 psychotherapeutic sessions, in combination with hypnotic, psychoanalytical, or psychodynamic psychotherapy (Eisner, 1997; Eisner & Cohen, 1958; Grof, 2001; Leuner, 1967). Psychedelic psychotherapy generally included one to three sessions with a psychedelic agent, greatly depended on set and setting, and was generally administered as a part of humanistic, existential, or transpersonal psychotherapy (Grinspoon & Bakalar, 1979; Grob, 1998, 2002; Grof, 1978, 1980, 1986; Grof & Halifax, 1976; Grof et al., 1973; Kolp et al., 2006, 2007, 2009; Krupitsky & Kolp, 2007; Pahnke, 1968, 1969, 1970; Richards et al., 1972, 1977, 1979; Walsh & Grob, 2005; Watts, 1973; Yensen & Dryer, 1993/1994).

Hallucinogen-assisted psychotherapy has been used for the treatment of people with a variety of psychological problems, including alcoholism and other addictive illnesses, anxiety and mood disorders, autism, psychosomatic diseases, criminal recidivism, and end-of-life issues, to name a few. The previous studies asserted that the most powerful results from treatment were induced by transpersonal (e.g., transcendental, mystical, spiritual, or religious) peak experiences (Pahnke, 1968, 1969; Pahnke, Kurland, Goodman, & Richards, 1969; Pahnke, McCabe, Olsson, Unger, & Kurland, 1969; Pahnke, Kurland, Unger, Savage, & Grof, 1970; Pahnke et al., 1970). This mystical peak experience (an ego-dissolving non-ordinary state of consciousness) induced by psychedelic substances can be in turn used to accelerate and enrich the course of psychotherapy. Depending on the therapist's school of thought, the ego-dissolving transcendental experience can be used as an adjunct to behavioral/cognitive, psychoanalytical/psychodynamic, humanistic/existential, or transpersonal psychotherapy. Each school of psychotherapy has its advantages and shortcomings. However, it seems that psychedelic-induced non-ordinary states of consciousness may be successfully used as an adjunct for several major schools of psychotherapy. It is thus understandable that, since the early 1970s through to the present time, a number of international psychiatric investigators have utilized ketamine-induced non-ordinary states of consciousness for psychotherapeutic treatment of various psychological problems, mental diseases, chemical dependencies, psychosomatic illnesses and personality disorders.

History of Ketamine Psychedelic Psychotherapy

Roquet was the first clinician to publish results from using ketamine for psychedelic psychotherapy, which occurred in Mexico (Roquet, 1975; Roquet & Favreau, 1981; Roquet, Favreau, Ocana, & Velasco, 1971). He combined traditional psychoanalytical techniques with the shamanic healing practices of indigenous Mexican Indian ceremonies and created a new approach to psychedelic psychotherapy that he called "psychosynthesis" (not the psychosynthesis developed by Robertos Assagioli, 1965). Roquet utilized ketamine 1.5 mg/kg (or approximately 125 mg IM) and treated primarily neurotic patients, although he described some success with character disorders and selected psychotic patients (Roquet, 1975; Roquet & Favreau, 1981; Roquet et al., 1971; Yensen, 1973, 1985). His therapeutic regimen also incorporated other psychedelic substances, such as LSD, mescaline, and psilocybin. Roquet used ketamine (and other psychedelic substances) in a group setting between 1969 and 1974 and applied his technique of psychosynthesis to approximately 150 patients (Yensen, 1985). He reported positive outcomes in 85% of his patients (Roquet, 1975; Roquet & Favreau, 1981; Yensen, 1985).

Roquet described four levels of possible experiences with ketamine (as well as with all other

psychedelic compounds he utilized). The first and most superficial level is a level of minor perceptual distortions. The second level is a level of wish fulfillment and fantasy (as the patient merely runs from problems with pleasant fantasies). Although patients can experience certain mystical states on this level, the experience usually does not yield true insight and results in only minimum reorganization of the personality. The third level is the level of existential anxiety and is often characterized by experiences of psychological death and rebirth. This level is frequently accompanied by the feeling of intense abreaction with catharsis afterward. The fourth level is the most intense, when the personality disappears completely, all previous points of reference are lost, and profound reorganization occurs. At this level, true life-altering experiences of a mystical nature can take place. Roquet regarded this level as essential to successful therapy and aimed to synthesize a healthy personality through the integrative qualities of this experience (Roquet, 1975; Roquet & Favreau, 1981; Yensen, 1973).

In Argentina, Fontana (1974) employed ketamine as an adjunct to psychotherapy for depression to facilitate regression to prenatal levels combining disintegration and death followed by progression to rebirth. He reported that ketamine allows therapists to introduce themselves into, and to correct, primitive experience through the relationship. Fontana emphasized the advantages of ketamine as making it possible to reach deep levels of regressions that had not been observed previously. However, we could not find the specific dose of ketamine he utilized, the type of psychotherapy he applied to his clients, or the specific number of the patients he treated with ketamine psychedelic psychotherapy.

In Iran, Khorramzadeh and Lofty (1973) administered ketamine as an "abreactive agent" to patients with various psychiatric illnesses (anxiety, depression, phobias, obsessive-compulsive neurosis, conversion reaction, hypochondriasis, and hysteria) and psychosomatic disorders (tension headaches and ulcerative colitis). Subjects were chosen from the inpatient population of a psychiatric unit of a university hospital in southern Iran. A total of 100 patients (61 males and 39 females) were investigated, ranging in age from 16 to 66. Patients with organic brain syndrome and psychoses were excluded.

Ketamine was administered intravenously in 3 dose ranges in Khorramzadeh and Lofty's (1973) work. The first group (25 patients) received 0.2 – 0.3 mg/kg body weight. Of the 25 subjects in this group, only one was reported as having a minimal response and 24 showed no response. These 24 were then given a higher dose of ketamine (0.4 – 0.6 mg/kg body weight) along with 72 others. A total of 95 demonstrated the abreactive response consisting of excitement, emotional discharge, verbalization of conflict, and emergence phenomena. Of the latter, all had facilitation of their psychotherapy and symptom relief. Group 3 included only one failure from the group 2 as well as 3 new patients. They received 0.7 – 1.0 mg ketamine/kg of body weight. According to the authors, all of these patients showed the abreactive response and had facilitation of their psychotherapy with symptom relief. In total, 74 subjects had intense visionary experiences; out of those, 51 patients recalled vividly painful childhood events regarding the key figures in that period. The complications were described as very minimal and included apprehension (2 subjects), nausea (3 subjects), and vomiting (2 subjects), which were treated with perphenazine (5 mg IM) with positive response.

Khorramzadeh and Lofty's (1973) subjects were seen 6 months after the injection. Only 9 patients were not doing well at this time, while ninety-one of the patients were doing quite well. After one year, 88 patients were still being observed and all except two were reported to be doing well (one had ulcerative colitis and the other tension headaches). They both requested another injection which was given and led to relief of symptoms for an unspecified period of time. They postulated that ketamine activated unconscious and repressed memories, while it could temporarily transport the patient back into childhood, reviving traumatic events with intense emotional reaction. They also concluded that ketamine's cathartic effect was related to its mind-expanding qualities and recommended the use of this chemical as an abreactive agent.

Khorramzadeh and Lofty (1976) later conducted another study to determine the types of ketamine-induced emergence phenomena and to discover any possible correlation between this phenomena and the type of personality involved. They used Eysenck's Personality Inventory (EPI) to evaluate the three dimensions of personality (Extraversion or E, Neuroticism or N, and Psychoticism or P) in patients who undertook ketamine anesthesia during surgery. A total of 606 patients were given a Persian adaptation of EPI the night before Ketamine anesthesia for operation. The maximum score accepted as normal for E and N

was 11, and for P was 5. When E fell below 5, it was considered an indication of Introversion. Out of 606 patients, 394, or 65%, showed no reaction. All of them had normal scores. The remaining 212 patients, or 35%, fell into the following seven groups, according to their various scores:

- Group E. Sixty-five patients (l0.7%) scored high in E (over 14). They experienced pleasant dreams, and some of them even felt they were in heaven among angels. Later questioning showed that they were all devoted Moslems. All of them expressed their willingness to undergo the experience again.
- Group N. Seventy patients (11.5%) had high scores in N (over 14). They all felt dizzy and related that to an experience of falls or rapid circular movements. They were indifferent to future use of the agent.
- Group P. Only 15 patients (2.4%) had high scores in P. They all reported body image distortions, loss of control over their limbs, and a sensation of a part of their body floating. In some the reaction was such that it had to be ended with perphenezine 5 mg IM. All refused to go through the experience again.
- Group NP. Fourteen patients (2.3%) scored high both for N and P. They had the combined experiences of groups N and P, making them feel terrified and most apprehensive. They were adamantly against future use of ketamine.
- Group PE. Ten patients (1.6%) scored high both in P and E. They screamed or laughed and had increased motor activity and some used foul language, while regaining consciousness. They all stated that they had a good time and the screaming was because of losing the pleasant feeling. They were willing to undergo the experience again.
- Group NE. Eighteen patients (2.9%) had high scores in N and E, and although they had the feeling of falling or circling, it was not at all unpleasant. One male patient stated that it was like a funny orgasm without ejaculation. They did not mind the future use of ketamine.
- Group Low E. Twenty patients (3.3%) scored 5 or lower in E. They cried and used profanity mostly directed at their close friends and relatives. After regaining consciousness, 10 of them had amnesia but the rest stated that they knew they were using profanity but could not control it. None wished to go through the experience again.

Khorramzadeh and Lofty (1976) reported that the EPI was found to be reliable in predicting the type of emergence phenomena. The reported results apparently showed that the majority of the patients (65%) did not experience emergence phenomena at all (those with normal scores). Of the remaining 35%, the majority had either pleasant (those with high scores in E, EP, and NE) or indifferent (those with high score in N) experiences. Only 8% had unpleasant experiences (those with high P and NP, and low E). This study supported that, in emergency situations requiring ketamine anesthesia, the drug may be administered without undue concern regarding the emergence phenomena, since only a small minority of patients had very unpleasant side effects. The study also documented that, in non-emergency situations, a simple questionnaire may help the anesthesiologist to select suitable candidates for ketamine induction.

Psychiatrist Stanislav Grof (1980) developed the most comprehensive theory of psychedelic psychotherapy from the transpersonal perspective. He wrote that psychedelics facilitate therapeutic experiences of symbolic death and rebirth of the ego, allowing clients to work through deep traumatic fixations in their unconscious. Grof designed a specific psychedelic psychotherapeutic approach, which he applied successfully with more than 750 patients. Although Grof primarily used LSD in his work, he acknowledged that ketamine holds great promise due to its affinity with dynamic systems. He reported that the psychoactive effect of ketamine is so powerful that it can catapult patients beyond impasses from previous LSD sessions to reach higher levels of integration (Grof, 1980).

Last in this regard, we want to mention the interesting recent work on DMT and spirituality, in the United States by psychiatrist Rick Strassman (2000, 2014). We see this as very complementary to our interest in ketamine.

Present Research on Ketamine Psychedelic Psychotherapy

In Russia, one of us (Evgeny Krupitsky) conducted the most comprehensive, rigorous scientific clinical research on ketamine psychedelic psychotherapy to date (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007;

Krupitsky et al., 1990, 1992, 1999, 2002, 2007). He began using ketamine as an agent for psychedelic psychotherapy in 1985 in the former Soviet Union. His early exploration of the use of ketamine as a psychotherapeutic agent employed a behavioral psychotherapy, specifically an aversive conditioning model for the treatment of alcohol dependence that was customary in Russia before the fall of the U.S.S.R. Krupitsky et al. (1992) combined traditional behavioristic methods of aversive therapy oriented towards creating negative associations between the use of alcohol and undesirable physical effects with earlier applications of psychedelic psychotherapy for treatment of alcoholism that sought to change an individual's attitude towards the use of alcohol but failed to imprint negative associations around the use of alcohol (Smith, 1964; Smith & Seymour, 1985). He created the affective contra-attribution (ACA) method that combined both of these approaches.

Initially, Krupitsky induced an aversive psychedelic experience by combining ketamine with bemegride (an analeptic agent with strong anxiogenic properties) in order to generate the frightening emotive experiences and produce strong negative emotions towards alcohol in the context of a terrifying hallucinatory experience. This forms the basis of the ACA method. These negative experiences are connected with the use of alcohol and with the alcoholic's life style. Later on, Krupitsky learned that those subjects who instead had an ecstatic transpersonal experience had equally remarkable, if not greater, beneficial outcomes and his work gradually shifted from a behavioral model to an existential and eventually transpersonal paradigm (Krupitsky & Grinenko, 1997).

Krupitsky initially used ketamine as an alternative treatment for alcoholism only. His original ketamine study demonstrated that KPP is highly effective in the treatment of alcohol dependence. Of 111 patients who received KPP in the first study, 69.8% were sober one year later, while only 24% in the control group remained abstinent during the one-year follow-up period (Krupitsky et al., 1992).

Krupitsky summarized his findings and documented that his patients became less anxious and depressed, more responsible and emotionally mature, with increased ego strength and positive changes in self-concept. His studies also showed that KPP brings about profound positive changes in life values and purposes, in attitudes to the different aspects of life and death, and rapidly accelerates psychospiritual development. Patients began to see other purposes, other values, other meaning and pleasures in their lives, grew more self-confident and balanced, more emotionally open and self-sufficient, and more responsible for their lives and the lives of their loved ones (Krupitsky & Grinenko, 1997).

Krupitsky and his team (1999) also examined the effectiveness of KPP for the treatment of heroin dependence. The team designed a double-blind randomized clinical trial comparing the relative effectiveness of a high psychedelic dose of ketamine (2.0 mg/kg IM) to a low non-hallucinogenic dose of ketamine (0.2 mg/kg IM) for the psychotherapeutic treatment of heroin addiction. The preliminary 6-month follow up demonstrated that a hallucinogenic (psychedelic) dose of ketamine was more effective than a non-hallucinogenic (sub-psychedelic) dose. Two-year follow-up data confirmed that the rate of abstinence in the high-dose ketamine group was significantly higher than that in the low-dose control group, while the corresponding rate of relapse was lower (Krupitsky et al., 2002).

This comprehensive study with heroin addicts, the first double-blind clinical trial of KPP conducted entirely within the evidence-based medical paradigm, clearly established that KPP significantly reduced the craving for heroin, considerably decreased the levels of anxiety and depression, markedly increased the level of spiritual development, and, to a great extent, enhanced understanding of the meaning and purpose of life. Interestingly, many of the measured change variables did not differ significantly between high and low dose groups. This suggests that the psychotherapy common to both groups played an important role in the observed effects. This could also be the effect of set and setting combined with a relatively low dose of ketamine. In addition, the study demonstrated that KPP produced few or no significant adverse reactions, and no subject participating in the study became addicted to ketamine (Krupitsky et al., 1999, 2002).

Krupitsky's most recent work employed single versus repeated sessions of ketamine-assisted psychotherapy in subjects with treatment-resistant heroin dependence who do not respond well to the initial treatment with KPP (Krupitsky et al., 2007). Fifty-nine detoxified inpatients with heroin dependence received one KPP session prior to their discharge from an addiction treatment hospital, and were then randomized into two treatment groups. Participants in the first group

received two addiction counseling sessions followed by two KPP sessions, with sessions scheduled on a monthly interval (multiple KPP group). Participants in the second group received two addiction counseling sessions on a monthly interval, but no additional ketamine therapy sessions (single KPP group). At one-year follow-up, survival analysis demonstrated a significantly higher rate of abstinence in the multiple KPP group. Thirteen out of 26 subjects (50%) in the multiple KPP group remained abstinent, compared to 6 out of 27 subjects (22%) in the single KPP group ($p<0.05$). Once again, no differences between groups were found in anxiety, depression, the severity of craving for heroin, or their understanding of the meaning of their lives. The data from this study provide some evidence that treatment-resistant patients who did not experience a mystical state of consciousness during the initial ketamine session may benefit from a second or even a third ketamine session. It appears that two or three repeated KPP sessions may work better and provide a higher rate of abstinence in heroin addicts than one KPP session, suggesting that increasing the number of KPP sessions might increase the efficacy of treatment.

Krupitsky's comprehensive clinical research of ketamine psychedelic psychotherapy has clearly documented that KPP is a safe and sometimes very effective treatment for alcoholism and opioid dependencies. It also proved to be efficacious in the treatment of stimulant dependence, as well as a very effective modality for the treatment of comorbid psychiatric conditions, such as posttraumatic stress disorder, neurotic depression, anxiety disorders, and avoidant personality disorders. In addition, his scientific work demonstrated that KPP might be effective for the treatment of phobic neurosis, obsessive-compulsive neurosis, and histrionic personality disorder (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007; Krupitsky et al., 2002).

Many of Krupitsky's patients developed a more spiritual approach to life through their transpersonal experiences. These encouraging clinical results occurred because of positive changes in the life values and purposes, relationships, and worldviews of these patients. They showed a transformation of emotional attitudes, a decrease in the level of inner discord, internal tension, discomfort, and emotional isolation; improved self-assessment; and a tendency to overcome the passive aspects of their personalities. These significant changes, along with a positive transformation of the patients' system of life values and meaning, as well as changes in their worldview, created a positive attitude toward a sober life and supported patients' ongoing stable sobriety (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

Unfortunately, changes in the regulations governing ketamine research in Russia brought Krupitsky's research efforts to a halt. When Krupitsky began working with ketamine psychedelic psychotherapy in 1985, psychedelics were not widely known in Russia and ketamine was a Schedule III drug in that country. After the collapse of the U.S.S.R., all drugs, including psychedelics, became much more available in Russia, ketamine included. Subsequently, ketamine abuse among Russian youth rapidly escalated from the late 1990s. The Russian government thus moved ketamine from Schedule III into Schedule II in 2002. Ketamine remains available only for anesthesia and conscious sedation at the present time in Russia. It became unavailable for the treatment of addictive disorders and psychiatric illnesses, and Krupitsky had to abandon his innovative work with KPP.

Technique of Ketamine Psychedelic Psychotherapy

Krupitsky has developed a specific and comprehensive course of KPP that comprises three main stages: preparation, administration, and integration (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007; Krupitsky et al., 1990, 1992, 1999, 2002, 2007). In the preparation stage, preliminary psychotherapy is carried out with patients, who are told that the psychedelic session may induce important insights concerning their personal problems, their system of values, their notions of self and the world around them, and the meaning of their lives. Patients are educated that all of these insights may lead to positive changes in their personalities, which will be important for healing their underlying problems and shifting to a sober lifestyle. At least five to ten hours of psychotherapy are provided before the ketamine session in order to establish the psychospiritual goal for the transpersonal experience and prepare the subject for the session. The therapist pays close attention to issues such as the patient's personal motives for treatment, goals for a sober life, and ideas concerning the cause of the disease and its consequences. The patient and therapist together form an individually tailored "psychotherapeutic myth" during this dialogue that creates an atmosphere of confidence and mutual understanding during the first stage of KPP. This then becomes the most important therapeutic factor responsible for the psychological content of the second stage of KPP (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

The second stage of this approach to KPP is the induction of the transpersonal experience through the administration of ketamine. Breakfast is omitted on the morning of ketamine administration, and all participants refrain from food and drink for at least eight hours prior to this experience. Patients are told that they will enter some unusual states of consciousness and are instructed to surrender fully to the experience. After the patient lies down in a comfortable supine position with eyeshades, ketamine is injected intramuscularly, in doses from 2.0 mg/kg to 2.5 mg/kg. The intramuscular route is preferred because the onset is more gradual and the psychedelic experience lasts longer. With an intravenous psychedelic dose (from 0.7 mg/kg to 1.0 mg/kg), the effect lasts only about 15 to 20 minutes, but with an intramuscular injection, it lasts from 45 minutes to an hour (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

With a background of specially chosen music, generally free-floating non-associative classical or New Age, the patient typically has a powerful non-ordinary state of consciousness, frequently resembling a mystical experience. After 45 minutes to an hour, the patient slowly comes back from the experience. During the recovery period, which takes from one to two hours, the patient begins to feel ordinary reality returning. At this point in the session, the patient usually begins to describe the experience and some discussion and interpretation is begun with the psychotherapist. After the session, the patient goes to rest. The patient is asked to write down a detailed self-report of the transpersonal ketamine experience that evening (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

The third stage is the integration of the ketamine-induced experience, which is carried out after the ketamine session. It is generally done in a group psychotherapy format, because the dynamic of the shared group experience appears more powerful and therapeutic than individual therapy alone. From three to five hours of psychotherapy are provided after the ketamine session to help subjects interpret and integrate their experiences during the session into everyday life. With the aid of the psychotherapist during the integration phase of treatment, the patients discuss and interpret the personal significance of the symbolic content of their ketamine-induced non-ordinary state of consciousness. This discussion is directed toward helping the patients make a correlation between their psychedelic experience and their intra- and interpersonal problems. The therapist assists the patients in the psychological integration of the spiritual transformation that can result from the direct transpersonal experience. This uniquely profound and powerful experience often helps patients to generate fresh insights that enable them to integrate new, often unexpected meanings, values, and attitudes about the self and the world (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

It should be explicitly pointed out that a ketamine-induced psychedelic experience may have only marginal and transitory beneficial effects in and of itself, no beneficial effects at all, or may be harmful when ketamine is used in uncontrolled settings recreationally. It can sometimes lead to significant medical problems and addiction (Jansen, 2000, 2001; Jansen & Darracot-Canckovic 2001; Ricuarte, 2005). The therapeutic relationship, as well as set and setting, are paramount to the effectiveness of ketamine psychedelic psychotherapy.

In order for the KPP sessions to cause positive transformative experiences, it is of central importance to carefully prepare patients for the KPP session, to attentively supervise them during the session, and to provide extensive psychotherapy after the session to facilitate the integration of the ketamine-induced transpersonal experience and to help patients personally accept insights gained during the KPP session (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

Present Use of Ketamine Psychedelic Psychotherapy

One of us, Dr. Eli Kolp is a bi-cultural psychiatrist and was originally trained in the former U.S.S.R. as a public psychiatrist. After Kolp requested that the Soviet authorities allow him to emigrate from the U.S.S.R., he was instead sent to work as an addiction specialist in the Moscow Alcohol and Drug Abuse Clinic #1, where Kolp learned how difficult the treatment of alcoholism in Russia could be. Even with the most intensive long-term treatment, which included multiple sessions of an unpleasant aversive conditioning, more than 75% of Russian alcoholics relapsed on alcohol within one year after completion of treatment.

After Kolp immigrated to the United States in 1981, he successfully re-trained as a private psychiatrist and began practicing general adult and geriatric psychiatry. Circa 1990, Kolp returned to the treatment of addictive illnesses, both in private and public sectors, where he directed various outpatient, residential, and inpatient programs specializing in the treatment

of alcohol, drug, and/or food addiction. He quickly learned that efforts to treat alcoholism in the American population are costly and have a low rate of recovery, as they do in Russia.

A previous meta-analysis of outcomes of treatment for alcoholism (Nathan, 1986) showed that different treatment methods did not appear to be associated with significantly different long-term outcomes. It was reported that treatment factors, including theoretical orientation, content, locus, and intensity of treatment revealed little or no difference in treatment outcome, despite great differences in costs. Although abstinence rates one year after treatment may reach 40% to 50% for persons with good treatment prospects (well-motivated, employed, sub-chronic alcoholics with a large network of support and substantial personal resources treated at private treatment facilities), typical abstinence rates for poorly motivated, unemployed, chronic alcoholics with a limited network of support and few personal resources seen at public treatment facilities were 25% or less. Rates of abstinence at and beyond the two-year mark are often less than 50% of the rates of abstinence at the one-year mark.

In the United States, Kolp, inspired by Krupitsky, thus began working towards utilizing ketamine psychedelic psychotherapy in 1994. His approach was explicitly meant to replicate Krupitsky's pioneering work and to extend it into another cultural context, the United States. With Krupitsky's guidance (while Krupitsky was working for one year with Krystal as a visiting scientist in the Department of Psychiatry at Yale University), Kolp designed a research protocol, entitled *The Ketamine-Assisted Therapy of Alcoholism*. The protocol was first approved by the Safety Committee of the James A. Haley Veterans Hospital in Tampa, Florida, and then by the Research and Development Committee of the Department of Veterans Affairs. It was further approved by the Research Committee of the Department of Psychiatry at the University of South Florida College of Medicine and the Institutional Review Board of the University of South Florida Health Science Center. Finally, by the end of 1996, the protocol was approved by the FDA, which issued to Kolp an Investigational New Drug permit. Unfortunately, the implementation of the protocol never materialized due to a lack of the institutional support and an absence of research funds. The Department of Veterans Affairs did not allow Kolp to use its facility and resources for this purpose, apparently because of the controversial nature of psychedelic psychotherapy at that point in time, which was somewhat prior to the recent "thaw" which has allowed some human work to be done with drugs such as psilocybin and MDMA (e.g., Friedman, 2006; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Griffiths, Richards, McCann, & Jesse, 2006).

Kolp was also unable to obtain funding for the study from multiple sources. It thus became necessary to abandon the planned, formal research study. Instead, Kolp employed ketamine psychedelic psychotherapy (KPP) in his private psychiatric practice. During the first several years (1994-1999), Kolp administered (KPP) to more than 70 patients. The patients were males and females, 21-64 years old, who identified alcohol as their drug of choice and satisfied the diagnostic criteria for alcohol dependence. Kolp followed all patients treated with KPP for as long as they continued the aftercare treatment, and he had individual and group sessions with them on a regular basis, from once a month to once every 3 months. In addition to being diagnosed with alcoholism, the vast majority of Kolp's patients (nearly 90%) had concurrent addictions (e.g., to caffeine, sugar, nicotine, cannabis, benzodiazepines, opiates, and amphetamines), and about half had coexisting psychological problems (e.g., generalized anxiety disorder, social phobias, primary insomnias, acute and repeated stress disorders, pain disorder, panic disorder, depressive disorder, posttraumatic stress disorder, tension and migraine headaches, somatization disorder, and chronic fatigue syndrome). As with Krupitsky's technique, Kolp's treatment modality explicitly relied on the transpersonal effects of ketamine to facilitate psychotherapeutic change. Kolp experimented with several different courses of treatment with KPP, ranging from a time-limited individual treatment on an outpatient basis to an intensive 1 to 3 week group treatment in the framework of a residential program. Kolp summarized his empirical clinical observations on KPP effectiveness for treating alcoholism and other coexisting disorders in his first report (Kolp et al., 2006).

After gaining extensive experience with KPP for the treatment of alcoholism, Kolp extended the inclusion criteria for KPP and began accepting patients with other drug dependencies and food addiction. Kolp also started utilizing KPP for the treatment of end-of-life anxiety in patients with terminal illnesses. He continued utilizing group psychotherapy in a residential setting

for treatment of addictive disorders and coexisting psychological problems. In addition, Kolp continued utilizing individual psychotherapy on an outpatient basis for treatment of existential anxieties in terminally ill people and selected patients with addictive disorders who did not wish to participate in a residential treatment program, or could not tolerate a group process.

During the second stage of his work with KPP (2000-2006), Kolp treated approximately 100 patients with various addictive illnesses (primarily alcoholism, opiate dependence, and food addiction), concurrent psychological diseases (mainly anxiety and mood disorder, acute and repeated stress disorders, and psychosomatic disorders), coexisting personality disorders, and existential anxieties related to the end-of-life issues. Kolp documented his empirical findings in a second report (Kolp et al., 2007). In addition, Kolp collaborated with Krupitsky and both authors published their combined experience and accumulated data on clinical research and empirical observation of the effectiveness of KPP (Kolp, Krupitsky, Friedman, & Young, 2009; Krupitsky & Kolp, 2007).

During the third stage of his work with KPP (2007 through the present), Kolp continued treating patients with various addictive illnesses, concurrent psychological diseases, and coexisting personality disorders. He also started accepting for KPP selected clients who had already resolved their addictions and major psychological problems and were looking for growth-oriented psychotherapy and lifestyle optimization.

In addition, Kolp began treating patients with chronic treatment-resistant depression (TRD), which is presently defined as a failure to respond to an adequate trial with two or three conventional antidepressants. Interestingly, the vast majority of the patients with TRD were not psychologically minded and had no interest in KPP. Instead, they desired to undertake only pharmacotherapy with a low sub-psychedelic dose of ketamine. In total, during the past 7 years, Kolp administered KPP to approximately 150 "psychologically-minded" clients with drug and food addictions, and ketamine pharmacotherapy to about 50 "pharmacologically-minded" patients with treatment-resistant chronic anxiety and/or depressive disorders.

Kolp also administered KPP in the same 3-stage format as was originally designed by Krupitsky: preparation, administration, and integration. Kolp always used a high psychedelic dose of ketamine (2.0 mg/kg – 2.5 mg/kg IM, or 150 – 200 mg IM) in order to both avoid an OBE and to specifically induce the near-death experience or, considered by Kolp as even more desirable, the ego-dissolving transcendental experience. Kolp disfavors an OBE for the same reasons that were previously discussed by Roquet and colleagues (1971, 1975) and Yensen (1973): most of the time the OBE simply represents the patient's wish fulfillment and the patient only runs from problems with pleasant fantasies. Although the OBE may resemble certain mystical states, the experience usually does not yield true insight and, in fact, may even have a negative effect on the ego, as illustrated by the following case study:

> C was a 52-year-old Caucasian female with a long history of binge alcoholism. She reported a stable childhood, with no history of physical or sexual abuse. C was raised as a Roman Catholic. However, she abandoned that denomination during her late teens, continuing as a non-denominational Christian.
>
> C began using alcohol at age 16, started drinking on a regular basis at age 18, and developed alcohol binges at age 25. Her binges lasted from 3-4 days to 2 weeks, every several weeks, with a consumption of nearly one liter of vodka a day during the binges. She undertook more than 10 various rehabilitation programs. However, she never had a stable remission (her longest remission lasted 7 months, including 2 months in a rehabilitation program). C did not wish to participate in a group residential program and elected an individual outpatient treatment. In addition, she did not follow strict preparatory guidelines (a whole food plant based diet, optimal hydration, daily meditation and exercise, limitation of screen time, etc.). Moreover, she continued using sugar, caffeine, and nicotine throughout the preparatory stage. Although she received 150 mg of ketamine IM, her ego remained well-preserved and she did not experience EDT, or, at least, NDE. Instead, she had an OBE that she described as "paradisiacal":
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> > *My mind left my body and I found myself in the Heaven … flying high above the silver and gold clouds … in the company of thousands of angels who were there to guide and protect me. The music was exceptionally lovely and we were ascending*

higher and higher … eventually arriving into the Garden of Eden. The angels showed me the beauty of their home and then helped me to soar directly to the throne of Jesus. His presence overwhelmed me and I started crying and laughing at the same time. I felt the Jesus' unconditional love and understood that all my sins were forgiven. He blessed me and I promised Him to never ever touch another drink of Vodka again. I then returned back into my body … feeling joyful and full of bliss … and I knew–with all my heart–that I got reformed forever.

She attended only one follow-up session and proudly reported that she had rejoined her church and started praying again on a daily basis. She insisted that her encounter with Jesus completely healed her from alcoholism and that she no longer needed to participate in an AA 12-step recovery program. C relapsed on alcohol 8 months later and committed suicide soon after the end of her 2-week binge.

Kolp quickly discovered that the OBE can be fascinating and gratifying for the ego, but it can sometimes have a rather low therapeutic potential outside of a long-term psychodynamic psychotherapy that requires repeated inductions of the OBE. Subsequently, Kolp's primary goal has been to induce the ego-dissolving transcendental experience, or at least the near-death experience, since both the NDE and EDT experiences more frequently generate not only a complete resolution of the patient's addictive illnesses and coexisting psychological problems, often after a single session, but may also cause instances of spontaneous healing from chronic psychosomatic illnesses (Fenwick & Fenwick, 1995; Grey, 1985; Kolp et al., 2007, 2009; Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007; Morse & Perry, 1992; Ring, 1980, 1984; Ring & Valeriano, 1998; Roud, 1990). In addition to its more specific healing potentials, the NDE and the EDT experiences may also rapidly accelerate patients' psychospiritual growth, broaden their worldviews, and generate a spontaneous spiritual transformation with a dramatic improvement of moral character (Kolp et al., 2007; Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

The primary factors that greatly influence the likelihood of these desirable NDE and EDT experiences are the dose of ketamine, the mindset of an individual prior to the ketamine session, and the session's setting. To reiterate, the mindset is the mental state that a person brings to the experience, such as thoughts, mood, personality structure, expectations, and worldviews. It is the most important part of KPP and basically stands for a rigorous preparation for the ketamine-induced experience. The setting is also very important and includes physical (the room's atmosphere) and social (feelings of the group's participants towards one another and toward therapist/therapists) components. The social support network is particularly important in the outcome of the ketamine-induced NOSC. The group and/or a therapist are able to control and guide the course of the experience, both consciously and subconsciously. Anxiety prior to the experience or a disagreeable environment may induce a frightening experience. On the other hand, curiosity and a positive attitude, together with a comfortable and safe place, are more likely to generate a blissful experience.

In addition to set and setting, the novelty of the psychedelic experience may be salient for successful problem resolution. Psychedelics are a unique class of drugs that produce intense effects unlike those of other drugs, and one's first "trip" can therefore be a profound and life-changing experience (as common wisdom says, "there is no second chance for the first impression"). Consequently, for those with extensive histories of psychedelic use, there is a diminished chance that a ketamine experience will be all that unique and transformative ("just another trip"), whereas for the novice psychedelic user, given proper mindset and setting, the experience can be profound.

Kolp believes that the most influential component of a successful KPP (in addition to dose, set, and setting) that can greatly increase the odds of the optimal EDT experience is vigilant preparation prior to the ketamine administration. Without a careful and laborious preparation, only about half of the patients may have an NDE (even with a dose of ketamine that is set to cause a near-death experience) and only 1 out of 20-25 patients may have an EDT experience. By attentively preparing the patients for a ketamine-induced experience through creating the spiritually-oriented mindset (as well as carefully controlling the setting), the likelihood of having an NDE becomes nearly universal. Meanwhile, the likelihood of an EDT experience can be increased from only 1 out of 20-25 patients to 3-4 out of 10 patients. Unfortunately, the EDT experience is very elusive and there is no guarantee of the EDT occurrence even with the most arduous preparation.

Whether the patient elects to participate in a residential group program or outpatient individual treatment, Kolp starts the preparatory period 6 weeks prior to the induction of the ketamine experience. During those 6 weeks, all patients participate in weekly group psychotherapy (unless the patient does not want a residential treatment, or cannot tolerate a group process; in that case the patient is engaged in a weekly individual psychotherapy). During the same 6 weeks, Kolp strongly encourages all patients to prepare the body and mind through partial fasting following a whole food plant based (WFPB) diet, optimal hydration, de-stressing through daily meditation, contemplation on the nature of the Self and God, limitation of "screen" time, and daily exercise. Kolp further suggests de-toxifying the body from all sedatives (such as sugar, alcohol, benzodiazepines, and opiates) due to their tendency to dull the mind and all psychostimulants (such as caffeine, nicotine, ephedrine, amphetamines) due to their tendency to aggrandize the ego.

In the experience of Kolp, fasting is a key aspect of the more acute preparatory process. The reasons why this is of assistance to the outcome remain speculative, but fasting has long been a part of the spiritual quest in many cultures and religions because it seemed to weaken the ties of the physical body to the material realm. Fasting can be total, abstaining from all food and beverages apart from water, or it can be partial. Kolp never asks patients to undergo a total fast. However, he highly recommends a partial fast and suggests abstaining prior to the ketamine session from highly refined simple carbohydrates (all sugary drinks such as soda pop and fruit juices, chocolate, doughnuts, cookies, cake, candy, etc.), highly processed complex carbohydrates (white bread, rolls, pasta, white rice, French fries, etc.), dairy products (milk, yogurt, sour cream, butter, cheese, ice cream, etc.), fatty "rich" foods (steak, bacon, salami, pastrami, hamburgers, cheeseburgers, etc.) and "junk" foods (chips, pretzels, crackers, pizza, etc.). Participants are encouraged to follow the WFPB diet, getting the majority of calories from vegetables, with some calories coming from certain whole grains, legumes, fruits, and nuts. During the fasting period, optimal hydration is strongly recommended by drinking one glass of water (no carbonated, caffeinated, or sugary drinks of any kind) every 2-3 hours during wakeful time.

To calm and prepare the mind, Kolp recommends taking a time out for daily meditation or mindfulness sessions. Ideally, participants would take twenty to thirty minutes each day for this practice. However, even ten to fifteen minutes daily is beneficial. Kolp also recommends spending fifteen to twenty minutes every day contemplating on the nature of the Self and the nature of whatever the person understands by the word "God" or the connectivity between the Self and the rest of the Universe, or a Higher Power as in the 12-step programs. Many participants find it helpful to keep a journal during this time to document their progress, including any regressions, in order to stay on track during this phase.

In addition, Kolp strongly advises de-stressing the mind by limiting "screen" time beyond that which is required for each individual participant's employment. Recreational screen time should be limited to less than two hours daily. Screen time includes, but is not limited to, computer use, watching television, playing video games, watching movies, and using smartphones.

Exercise is recommended at least five days a week for a period of forty-five to sixty minutes at a time. Kolp recommends low impact isotonic exercises such as deep stretching or yoga; however, any type of exercise is beneficial.

Although the preparatory guidelines may seem strict, this conscious preparation of the body, mind, and spirit prior to the administration of ketamine is seen by Kolp as increasing the likelihood of having either a classic NDE or distinct EDT experience. In Kolp's experience, after a detailed, vigilant, and focused preparation, almost 50% of participants have a classical NDE and nearly 35% participants have a highly desirable EDT experience. Unfortunately, even with the most arduous preparation, approximately 15% of participants still have a standard OBE. Most of them are the patients who had a very high tolerance to sedatives (e.g., sugar, alcohol, benzodiazepines, barbiturates, and opiates), severe control issues (they are simply unable or unwilling to surrender to the existential or transpersonal experience), persistent difficulties in maintaining long-term interpersonal relationships, and those with dogmatic beliefs in an authoritative or critical God.

After 6 weeks of an outpatient preparation and detoxification as well as 6 weekly psychotherapy sessions, the patients are placed in a structured residential setting for the second stage of treatment—the administration of ketamine-induced non-ordinary states of consciousness.

The length of a residential component varies from 1 week (growth-oriented program) to 3 weeks (addiction rehabilitation program). The one-week growth-oriented residential program offers 30 hours of psychoeducational and encounter groups, existential and transpersonal group psychotherapies, and interactive classes and didactic lectures. The three-week rehabilitation program for the treatment of food and drug addiction provides the same 30 hours of analogous psychoeducational and encounter groups, existential and transpersonal group psychotherapies, and interactive classes and didactic lectures. In addition, it provides another 60 hours of various life skills training such as communication skills, problem solving skills, relapse prevention, relationship skills, anger management, and decision-making, as well as training in optimal lifestyle and advising health issues, nutrition education with food purchase and preparation, non-verbal therapies, such as art therapy and music therapy, in order to provide the patients with alternative means of self-expression, problem resolution, and motivational enhancement. Those patients who opt out of a residential component of a treatment program receive the administration of ketamine in an outpatient setting, without the benefits of an intense group process of a residential program.

Whether ketamine administration is performed in an outpatient office, or in a residential center, Kolp recommends both settings have comfortable, scenically pleasant, home-like atmospheres. Breakfast is omitted on the morning of ketamine administration, and all participants refrain from food and drink from midnight through the ketamine-induced experience. The ketamine solution is administered via a brief intramuscular injection, rather than an intravenous administration requiring the use of an IV line, adding to the comfort of each patient. After the injection, the patient wears eyeshades, is instructed to fully surrender to the ketamine-induced experience, and beautiful, evocative music starts playing to assist with relaxation and immersion into the experience.

The NOSC lasts from 45 minutes to an hour under these conditions and then the patient slowly comes back from the experience. During the recovery period, which takes from one to two hours, the background composition changes from a free-floating non-associative music to an inspirational guided imagery meditation to affirm the patient's sought after transformation. When patients returns to an ordinary state of consciousness, they are asked to describe the experience, and some limited discussion and interpretation is begun with the psychotherapist. After the session, the patient goes to rest and is asked to write down a detailed self-report of the ketamine-induced transpersonal experience during the second part of the day.

The integration of a ketamine-induced experience starts on the evening after the ketamine session and continues throughout the rest of the residential program. After the end of a residential component of the treatment, all patients continue weekly group psychotherapy sessions on an outpatient basis for 3 additional weeks. The patients who elect to participate in an outpatient individual treatment also receive 3 weekly individual psychotherapy sessions during the integration part of the treatment. Afterward, Kolp provides follow-ups every 6 months for all patients treated with KPP for as long as they continue to participate in aftercare.

With these in depth, challenging preparatory and aftercare guidelines, Kolp was able to increase the effectiveness of KPP from 70% reported by Krupitsky (1992, 1997) to approximately 85% previously reported by Roquet (1975) and Yensen (1985). So far, the longest observed remission has been for 12 years (the patient undertook a 3-week residential treatment program in 2002), as illustrated by the following case study:

> B was a 47-year-old Eurasian male who identified himself as a food addict. He reported no childhood trauma and described his nuclear family as very loving and supportive. B was raised as a Methodist, but changed his religious identification to a non-denominational Christian during his late teens and eventually began identifying himself as "spiritual but not religious" during his early 30s. He described himself as a "steak and potato man" and was proud of himself for never having a dessert. B had 6 feet 4 inches height and 220 pounds weight by age 18 and remained very fit throughout his mid-20s due to a very strenuous athletic involvement (a football player in high school and 6 years of active duty service in the Marine Corps). After an honorable discharge from the armed forces at the age of 26, he became employed as a manager of a fast food restaurant.
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> B described himself as a compulsive overeater, who never attempted to compensate for his bingeing with purging behaviors such as fasting, laxative use, or vomiting. He did exercise a good deal through his

early 30s. However, he eventually stopped working out and developed a sedentary lifestyle. In addition, he became engaged in "grazing" behavior and started picking at food throughout the day.

B's food preference was for fats and flour products, which he consumed three times a day, in addition to snacking between his major meals. His tolerance slowly increased and by his late 30s, his typical breakfast consisted of one 8-ounce sirloin steak, two big baked potatoes with sour cream, 4 scrambled eggs, a couple of sausages or 2 slices of ham, and a half dozen biscuits with butter. His lunch and dinner were equally impressive, always including large amounts of meats, bread, and butter. In addition, B had 3-4 self-made sandwiches between his main meals, which he prepared from a slice of ham or bologna meat, a slice of cheese, and 2 slices of white bread with butter. Once a month he treated himself with a 30-ounce strip sirloin at a steak house. B was a participant in an April 2000 survey, who would not give up meat for a week even if he were paid a thousand dollars to do so.

By the age of 40, B's weight reached 300 pounds. He was already diagnosed with hypertension, type II diabetes, hyperlipidemia, osteoarthritis, and sleep apnea. He had to take eight medications a day and his primary physician repeatedly warned him that he was a few years away from a stroke or a heart attack. At that point B started taking some action and began dieting, but always unsuccessfully. He would stay on a diet of the season for a few weeks and sometimes drop several pounds in weight. However, each time he resumed his compulsive overeating.

B joined Overeaters Anonymous (a 12-step recovery program based on the principles of Alcoholics Anonymous, which is also known as The Fellowship) at age of 42, but left the program after a year ("too much praying, but no spiritual awakening"). He also briefly tried Food Addicts in Recovery Anonymous (an alternative 12-step based program) and had no problems with completely abstaining from sugar, but could not abstain from the flour products longer than several weeks. In addition, he resented weighing and measuring all his meals and could not abstain from snacking between meals. B undertook a sleeve gastrectomy at age of 44, which helped him to decrease his weight to 250 pounds. However, he managed to "re-feed" himself within 2 years after the surgery. By the time he applied for treatment with KPP his weight was 310 pounds.

B was willing to stop eating meat and dairy products for 6 weeks prior to a ketamine session and agreed to abstain from highly refined and/or highly processed food for the same period of time. He reported severe cravings for fats and flour during the first 3 weeks. However, he was able to remain abstinent from the prohibited items. B actively participated in all groups, meditated twice a day, and started walking for 30 minutes every other day. Unbeknown to his therapist and the group, B sneaked out of the residential facility the evening prior to the administration of ketamine in order to have his "last supper," a veal parmigiana dish. The following morning B received 250 mg of ketamine IM and had a very frightening NDE that he described as "hellish":

> *I got out of the body and initially rejoiced the freedom of leaving my fat and sick body. Within a minute or two though my mind started dissipating and it scared me very much. I remember thinking: I am really dying … it is the end of my life … oh, no, no … please make it stop. The mind completely gone and all that remained was a soul … silent, sad and lonely … rapidly falling into the abyss of nothingness. At some point the movement ... stopped and the soul became motionless in the middle of the void. All of the sudden, my entire life began getting replayed and the soul was despondently observing my Earthly life of a glutton … a hungry sponge devouring countless living beings out of a lust for taste. The feeling of sorrow became resilient and the last conscious awareness was terrifying—if the Hell and the Heaven do, in fact, exist, the soul definitely belongs to the Hell.*
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> *As soon as my soul came to this conclusion, it got immediately sucked deep into an infinite ocean of unconditional sorrow and became that veal calf … taking away from the mother … suspended in a stall … restricted in movements … without seeing a sky and the trees … sensing that something is terribly wrong … that it is not how life is supposed to be lived … tormented and very miserable … finally going through a cruelty of a slaughterhouse … hanged upside down … skinned*

while still being alive. The soul's suffering became repetitive … re-living life of all animals that my body consumed and my mind adored … again and again … life after life … with no end at all. It seemed like the soul has been tortured for thousands if not millions of years before the mind re-emerged and then re-entered the body. My whole essence was screaming —no more carnivorous lifestyle … no more causing suffering and death to God's innocent creatures.

B has continued to conscientiously participate in aftercare since the completion of his treatment and completely abandoned eating any animal products, both meat and dairy. He continued meditating daily and restarted exercising on a regular basis. B did not give up eating biscuits and potatoes (no butter and no sour cream), but he started limiting the consumption of flour and starches to once a week, eating only two biscuits and one potato on the weekends. Within 2 years, his weight stabilized at around 200 pounds and has remained constant since. The number of the medications has decreased from 8 to 1 and his hypertension, type II diabetes, hyperlipidemia, and sleep apnea have completely resolved.

Although the above case is rather exceptional, the vast majority of the patients treated with KPP do develop a stable remission, lasting from 2-3 to 5-7 years and longer. Kolp, like Krupitsky before him, has repeatedly observed a dramatic improvement in patients' overall bio-psycho-socio-spiritual functioning, including rapid optimization of a personal lifestyle, decreased levels of inner conflicts and emotional isolation, enrichment of interpersonal relationships, resolution of existential death anxiety, positive changes in the life values and purposes, broadening of the worldviews, and acceleration of psychospiritual growth, through his approach to KPP.

Possible Mechanisms of the Effectiveness of KPP

Krupitsky previously reported that ketamine increases delta and theta activity in the cortex, evidencing limbic system activation as well as limbic-cortex interaction (Krupitsky & Grinenko, 1997). It was further documented that ketamine exerts its effect through a functional and electrophysiological dissociation or disconnect between the thalamo-neocortical and limbic areas of the brain (Green & Krauss, 2004a, 2004b; Mistry & Nahata, 2005).

Therefore, the Russian group including Kolp hypothesized that ketamine's underlying mechanism of action on the brain is the blockade of the thalamo-cortical projections and the activation of the interactions between frontal cortex and limbic structures, which results in a specific hyperfrontal metabolic pattern in the human brain, associated with ketamine-induced psychedelic experience (intense visionary experience and ego-dissolution). The thalamus' primary function is to relay sensory and motor signals to the cerebral cortex; the frontal cortex is responsible for cognitive processing of information (conscious mind); and the limbic system is the brain's center of emotions (unconscious mind). Thus, ketamine blocks transmission of incoming signals from all sensory modalities, including signals from the outer world and one's own body, and reinforces the interactions between the so-called cognitive and emotional minds. In other words, ketamine appears to disconnect the self from so-called objective reality, ties self-aware and unaware levels of mind in a closed loop, and removes a filter between conscious mind and unconscious mind, resulting in a profound waking dream that bears a remarkable resemblance to OBE, NDE, or EDT experiences.

The ketamine-induced non-ordinary states of consciousness seem to generate a different level of self-identification. Kolp describes that as, during OBEs, self-identity switches from "I am Body" to "I am Mind," while during NDEs the self-identity becomes more similar to "I am Soul" and during the EDTs more like *Unio mystica* or mystical union in which self-identity further progresses to "I am God." At no time, of course, is it suggested in KPP that the Soul and/or God experiences constitute any proof of the existence of any specific theological concept. These psychedelic experiences are subjective phenomena that cannot be easily, if ever, scientifically objectified, and they certainly do not prove the existence of any transcendental reality. Nevertheless, for reasons that remain speculative, having the uniquely profound and powerful mystical experience can significantly contribute to broadening attitudes about the self and the world, positive changes in life values and purposes, resolution of existential death anxiety, and rapid acceleration of spiritual transformation.

In 1962, Pahnke (1962, 1968, 1969; Pahnke et al., 1970) conducted the double-blind "Marsh Chapel Experiment" (a.k.a. the "Good Friday Experiment") investigating whether a psychedelic agent (psilocybin) would cause a genuine mystical experience in religiously

predisposed subjects. Virtually all members of the psilocybin group (graduate degree divinity students) reported having profound religious experiences and the faculty of the Harvard Divinity School concluded that a psychedelic agent can indeed facilitate such mystical experiences.

Twenty-five years later, Doblin (1991) traced seven theological seminary students participating in the Good Friday Experiment and reported that all of the psilocybin subjects continued considering that their original religious experience had a genuineness in terms of mystical nature and characterized it as a high point of their spiritual lives. One of these students was religious scholar Huston Smith, an author of several textbooks on comparative religion, who later on described his original psychedelic experience as the most powerful homecoming he had ever experienced (Smith, 2001).

In 2002, a group of investigators at Johns Hopkins University conducted a more rigorously controlled study similar to the Good Friday experiment (Griffiths et al., 2006). The study's participants were hallucinogen-naïve adults who reported regular participation in religious or spiritual activities. The study compared psilocybin (30 mg) and methylphenidate (40 mg) using a double-blind between-group, crossover design. Thirty volunteers received 30 mg of psilocybin and 40 mg of methylphenidate in counterbalanced order. Two or three sessions were conducted at 2-month intervals. To obscure the study design, 6 additional volunteers received methylphenidate in the first 2 sessions and un-blinded psilocybin in a third session. The 8-hour sessions were conducted individually. Volunteers were encouraged to close their eyes and direct their attention inward. The study's investigators documented that 67% of the participants who received psilocybin experienced powerful NOSC that had similarities to naturally occurring mystical experiences. Furthermore, those drug-induced mystical experiences were rated by volunteers as having great personal and spiritual significance that resulted in sustained positive attitudes and behavior that were corroborated by ratings from friends and family.

Sixteen months later, the same group of researchers at Johns Hopkins University completed a follow-up to their original psilocybin study (Griffiths et al., 2008). Two thirds of the study participants continued rating the psychedelic-induced experience as among the top most meaningful experiences in their lives. Sixty-four percent of the participants reported that the experience increased well-being and life satisfaction, and 58% met criteria for having had a "complete" mystical experience. Seventeen percent indicated that it was the most meaningful and significant experience, while none of the participants rated the experience as leading to decreased well-being or life satisfaction. The researchers concluded that the mystical aspect of the experience was crucial in achieving positive therapeutic outcomes, and they recommended additional therapeutic trials with hallucinogens.

Kolp thinks it is evident that an ego dissolution during psychedelic-induced mystical (transcendental, spiritual) peak experience is perceived by healthy volunteers and mentally ill patients alike as transcending their individual body restrictions and generates a psychological sense of security which extends beyond the impermanence of the finite corporeal body. Successively, the individuals can better cope with the prospect of the yet to come death and demonstrate a long-lasting resolution of existential death anxiety (Cohen, 1965; Griffiths et al., 2006, 2008; Grinspoon & Bakalar, 1979; Grob, 1998, 2002; Grof, 1978, 1980, 1986; Grof & Halifax, 1976; Grof et al., 1973; Kast, 1966a, 1966b; Kast & Collins, 1964; Kolp et al., 2007, 2009; Krupitsky & Grinenko, 1996; Krupitsky & Kolp, 2007; Krupitsky et al., 1992; Pahnke, 1968; Pahnke et al., 1970; Richards et al., 1972, 1977, 1979; Walsh & Grob, 2005; Watts, 1973; Yensen & Dryer, 1993/1994). The following case study demonstrates the efficacy of ego-dissolving transcendental experience in the treatment of a patient with chronic depression, recurrent headaches, and combined opioid and barbiturate dependence:

> M was a 34 year-old Hispanic American female who had been suffering from chronic depression since her puberty. In addition, she developed the onset of recurrent headaches within 2 years after the commencement of her marriage at the age of 22. She was raised as a non-denominational Christian and changed her self-identity to "spiritual but not religious" during her early 20s. She reported no history of physical and/or sexual abuse during her childhood, but acknowledged a long history of an ongoing repeated stress due to a hapless marriage (she described her husband as a "patriarchal male chauvinist pig"), 2 children of ages 11 and 9 with conduct disorder and ADHD (whom she referred to

as "little terrorists"), and a demanding full-time job with an "awful boss."

M began psychiatric treatment at the age of 16 and and had already been prescribed many antidepressants, including five SSRIs (fluoxetine, paroxetine, sertraline, citalopram, and escitalopram), three SNRIs (venlafaxine, duloxetine, and desvenlafaxine), one NRI (bupropion) and one NaSSA (mirtazapine). Although she responded well to the treatment with her first SSRI and first SNRI (both times the remission lasted for 9 and 6 months respectively), the efficacy of antidepressant treatment eventually became marginal. M also started treatment with a neurologist at the age of 24 and was treated with several anti-migraine medications, including sumatriptan, metoprolol, topiramate, gabapentin, rizatriptan, and pregabalin, all with limited results.

At the time of her initial evaluation for KPP treatment, M was taking a combination of bupropion (300 mg in the morning), mirtazapine (45 mg at bedtime), and Fioricet (codeine 30mg, butalbital [a barbiturate] 50mg, acetaminophen 300mg, and caffeine 40mg) which she took as 2 capsules 4 times a day (240 mg of codeine and 400 mg of butalbital daily). She continued complaining of chronically depressed mood (she scored 28 points on the Beck Depression Inventory) and recurrent headaches (3–4 times a week, lasting for several hours).

M elected to participate in a group residential program and agreed to get detoxified from both sedatives (codeine and butalbital) and both antidepressants (bupropion and mirtazapine) since her medications "did not work anyway." In addition, she dutifully followed strict preparatory guidelines (a whole food plant-based diet, optimal hydration, daily meditation and exercise, limitation of screen time, and contemplation on the nature of the Self and God). After successful preparation on an outpatient basis, M was admitted to a residential program where she became actively engaged in an intensive group process. She received 150 mg of ketamine IM and reported the following EDT experience:

> *My body became dissolved as an icicle in a hot water and my mind began steadily expending as an inflating balloon. First, I got aware of the surrounding space around me and actually became the growing trees … and birds … and animals … and other people … in the range of 300-400 yards around me. This expansion did not stop at it and my mind continued progressively getting larger and larger … until it embraced the entire Earth and I became aware that I am a part of the Great Mother Gaia. At that point my individual mind disappeared and became transformed into collective mind. The collective mind continued rapidly expending to the entire Solar system … then to the entire Milky Way galaxy … and eventually to the entire Universe. The individual awareness shifted to the awareness of the Universal Mind and my personal Soul became a part of the Universal Consciousness. God and I are One and We are omniscient, omnipotent, omnificent and omnipresent. The experience seemed lasting for the eons … and all that time the awareness remained "everything is exactly as it should be" … "We are all One" … "everything is perfect" … "everything is perfect" …*

M continued in aftercare for 2.5 years until she and her family relocated to another state. She reported that her chronic depression had finally resolved and her recurrent headaches were completely gone. M also became actively engaged in ongoing family psychotherapy and reported marked improvements in her relationships with her husband and children, as well as improvements in her other interpersonal relationships. She continued exercising and practicing meditation on a regular basis, stopped consuming animal products, and began volunteering in a local charity.

M's case represents a typical KPP treatment outcome among those patients who experienced an ego-dissolving mind-expanding transcendental experience.

Antidepressant Effects of Ketamine

The low dose of ketamine used for analgesia and anxiolysis as well as the medium dose of ketamine used for conscious sedation can reliably produce brief but robust antidepressant effects. Various investigators started publishing reports documenting antidepressant effects of ketamine in the early 1970s. These earlier studies, performed from the 1970s through the 1990s, utilized ketamine in medium doses and generally attributed anxiolytic/antidepressant responses to an overall psychological improvement following the

induction of NOSC, a specific phenomenon called "psychedelic afterglow." This psychedelic afterglow state consists of positive physical and psychological changes, including increased psychological clarity, feelings of being cleansed, increased confidence, feeling of happiness and well-being, state of inner peace, feelings of detachment, motivation to improve oneself, and strong feelings of empathy for everyone. The afterglow state was thought to be induced by the psychedelic peak experience and reported to last from several days to several weeks and longer (Adamson, 1985; Bolle, 1985, 1988, 1992; Grossbard, 1989; Fontana, 1974; Khorramzadeh & Lofty, 1976; Krupitsky, 1993/1994; Krupitsky & Grinenko, 1996, 1997, 1998; Krupitsky et al., 1992; Moore & Altounian, 1978; Roquet, 1975; Roquet & Favreau, 1981; Roquet et al., 1971; Yensen, 1973).

However, it was also long recognized that ketamine was likely to acutely improve mood secondary to its effects on, for example, the dopamine system, which have some commonalities with amphetamine and cocaine, and there was certainly long-standing speculation as to a neurochemical basis for ketamine improving mood for up to a week, with lack of a post-stimulant crash being attributed to such possibilities as the lingering presence of active ketamine metabolites and/or gene induction (summarized in Jansen, 2001.) In this context, it is of note that the original Maudsley monograph describing amphetamine psychosis warned against attributing mental state changes to anything other than amphetamine while the metabolites could still be detected in the urine, and that the metabolites could sometimes be detected for at least a week (Connell, 1958), as is sometimes the case with ketamine.

The general trend changed with a formal study done by Krystal's group of investigators who reported that research subjects with symptoms of depression showed a dramatic antidepressant response to an administration of low sub-psychedelic doses of ketamine (Berman et al., 2000). It is interesting to note that the original purpose of this study was not to research the antidepressants effects of ketamine but to assess its cognitive effects on subjects with mental illness. The antidepressant effect of ketamine was apparently not expected by this group (Brown, 2007). Some similar studies have replicated these findings and confirmed that low doses of ketamine can produce a rapid antidepressant effect lasting from 1-2 days to 1-2 weeks (Kudoh et al., 2002; Ostroff, Gonzalis, & Sanacora, 2005). These results would probably not have been a surprise to most non-medical and "recreational" users of the drug, who have long reported elevation in mood for up to a week (summarized in Jansen, 2001).

These earlier reports seemed to have only a limited impact until a study was conducted at the National Institute of Mental Health (Zarate et al., 2006). This randomized controlled trial was specifically conducted in subjects with TRD, including some patients who had not responded to electroconvulsive therapy. The study provided evidence that a single sub-anesthetic dose of ketamine may provide rapid but non-sustained relief of depressive symptoms.

Since publication of this study, further reports have confirmed the efficacy of ketamine for the treatment of major depressive disorder and the depressive phase of bipolar disorder (aan het Rot et al., 2010; Bjerre & Fontenay, 2010; DiazGranados et al., 2010; Ibrahim et al., 2012; Liebrenz et al., 2007, 2009; Murrough et al., 2011, 2012; Rasmussenet et al., 2013; Rot et al., 2008; Zarate et al., 2012, 2013). Most recent studies have used a low sub-psychedelic dose of ketamine (0.5 mg/kg) administered via IV infusion over 40 to 60 minutes (aan het Rot et al., 2010; Bjerre & Fontenay, 2010; DiazGranados et al., 2010; Glue, Gulati, Le Nedelec, & Duffull, 2011; Ibrahim et al., 2012; Liebrenz et al., 2007, 2009; Murrough et al., 2011, 2012; Rasmussen et al., 2013; Rot et al., 2008; Zarate et al., 2006, 2012, 2013), and one study utilized a low sub-psychedelic dose of ketamine (1 mg/kg) via IM administration (Glue et al., 2011). The number of ketamine administrations has varied from one to six (aan het Rot, Zarate, Charney, & Mathew, 2012).

There are also reports documenting the effectiveness of ketamine pharmacotherapy in the treatment of eating disorders (Mills, Park, Manara, & Merriman, 1998) and obsessive-compulsive disorder (Rodriguez et al., 2013). Murrough and colleagues examined the efficacy of repeated ketamine infusions on the length of post-treatment remission (Murrough et al., 2012). The study's subjects underwent a washout of antidepressant medication followed by up to six IV infusions of ketamine (0.5 mg/kg) administered three times per week over a 12-day period. Seventy-one percent of the patients developed a remission. However, the median time to relapse after the last infusion of ketamine was only 18 days. Some researchers have thus

been adopting a maintenance strategy (Messer & Haller, 2010). There have been reports of oral (Irwin & Iglewicz, 2010; Paslakis, Gilles, Meyer-Lindenberg, & Deuschle, 2010) and sublingual (Lara, Bisol, & Munari, 2013) ketamine as an effective maintenance antidepressant. Since intranasal ketamine has been already used as an effective maintenance sedative and analgesic (Bahetwar, Randey, Saskena, & Chandra, 2011; Reid, Hatton, & Middleton, 2011), this technique is also being developed as both an initial and maintenance treatment of major depression (Lapidus et al., 2014). These 3 modalities—oral, sublingual, and intranasal—are emerging as the preferred delivery methods of a ketamine maintenance treatment.

It is unknown how many persons who take non-prescribed ketamine (i.e., non-medical and recreational users) are actually taking the drug to self-medicate what amount to depressive disorders. It is also unknown how many clinical practitioners in the United States have administered ketamine to patients with TRD, but general correspondence suggests a marked increase. An internet search identified an on-line organization (Ketamine Advocacy Network; KAN) that has a list of "ketamine doctors" in the United States who are performing the ketamine administration procedure (www.ketamineadvocacynetwork.org). At the time of writing this paper, KAN was listing 17 physicians from 3 specialties, including 10 psychiatrists, 5 anesthesiologists, and 2 neurologists. All physicians are providing both the initial infusion of ketamine to rapidly relieve depression and a maintenance therapy to lengthen a remission after the symptoms of depression re-emerge. Sixteen physicians administer IV infusions of ketamine, and 1 psychiatrist administers IM injections. One psychiatrist is offering a post-infusion maintenance treatment with transcranial magnetic stimulation, one anesthesiologist is offering maintenance treatment with intranasal and oral ketamine, and one neurologist is offering an intranasal maintenance treatment.

It is understandable why the majority of known ketamine providers have used IV infusions. All initial research studies that reported a robust anti-depressant effect of ketamine were using IV infusions of ketamine. However, IV infusions are partly the preferred delivery methods in a research setting because an IV line provides access for collecting blood samples to measure various biochemical markers before, during, and after the procedures. Outside the research setting, IV infusions may offer no particular advantage, and seem unlikely to be more beneficial than IM injections. This fact was emphasized by the initial group of formal researchers (aan het Rot, Zarate, Charney, & Mathew, 2012), who pointed out that previous research documented that IV administration of conventional antidepressants did not support increased efficacy over oral administration (Moukaddam & Hirschfeld, 2004).

From the viewpoint of a physician practicing in a clinical setting, the IV infusions have many disadvantages. They are supposed to be performed in a hospital setting and to require the presence of an anesthesiologist, decrease the duration of therapeutic NOSC from 45-60 minutes to 20-25 minutes (unless performed as a continuous drip), and can increase the procedure's cost to the patients from approximately $400 per IM administration to around $2,000 per IV infusion, or more. Meanwhile, ketamine administration for treatment of mental illnesses remains an "experimental" procedure and its cost is not yet being covered by any medical insurance company, forcing non-research patients in the United States to bear the cost. In addition, IV infusions needlessly medicalize the procedure and, consequently, may increase the chances of a frightening experience. It has been suggested that IV ketamine infusions should perhaps be reserved for emergency room treatment only, where acutely suicidal depressed patients frequently present themselves (Larkin & Beautrais, 2011), although it is likely that even in this context, IV will eventually be shown to have no powerful advantage over IM when all the costs and benefits are weighed, as has gradually been demonstrated in psychiatric ICU hospital practice for benzodiazepines and antipsychotics, in which context giving the medicines as an IV injection is fading away in English-speaking countries (e.g., Taylor, Paton, & Kapur, 2012).

Other practitioners have already started utilizing IM injections of ketamine as the preferred treatment. A leading article in the January 2013 issue of *Psychiatric Times* (Kaplan, 2013) described a ketamine treatment program at the University of California San Diego (UCSD) Medical Center, directed by David Feifel, an associate professor in the Department of Psychiatry. Feifel recommended starting with the initial infusion to assess the length of a remission. Those patients who demonstrate at least one week of a stable remission are then referred for a maintenance treatment with repeated administrations of a low intramuscular

dose of ketamine (0.5 mg/kg) and no more frequently than once every 2 weeks. Feifel has begun utilizing an IM administration because of its practicality and cost effectiveness. He shared that when the UCSD program first started, anesthesiologists were required to give the intravenous ketamine infusions in an acute care setting, with the costs of IV procedures around $2,000 per infusion; in contrast, IM administrations are now given by nurses, with an attending physician available during the procedure, and the cost went down significantly (Kaplan, 2013).

Ketamine psycho-pharmacotherapy is rapidly gaining momentum. The FDA awarded the breakthrough therapy designation for the development of intranasal ketamine for treating depression (a definition of breakthrough therapy is a drug that treats a serious or life threatening disease and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development). If a drug is designated as breakthrough therapy, the FDA will expedite the development and review of such a drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and the FDA will either grant or deny the request. This is the first time this special designation, usually reserved for drugs targeting a lethal epidemic or a deadly form of cancer, has been awarded for the development of a medication for a mental disorder.

A key remaining question is the duration of ketamine's effect, which significantly varies not only from person to person, but also from treatment to treatment for the same person. At times, the effect only lasts a day or two and at other times, the effect lasts 1-2 weeks, or even a month.

The Biological vs. Psychological and Transpersonal Effects of Ketamine

As noted, some of the earlier ketamine studies attributed the anxiolytic and antidepressant post-treatment effects to "psychedelic afterglow" following the induction of NOSC. Contrary to the earlier reports, most of the recent studies ignore the psychological effects of ketamine-induced altered states of consciousness and appear to largely dismiss these psychological phenomena, particularly those of a transpersonal quality which are presented mostly as an undesirable side-effect. For example, Arun Ravindran, psychiatry professor at the University of Toronto and chief of mood and anxiety disorders at Toronto's Centre for Addiction and Mental Health, will be leading a study specifically exploring oral and intranasal routes of ketamine administration. In a recent interview with *The New York Times* (October 10, 2014), Professor Rivandran was referring to ketamine-induced psychological phenomenon as an unwanted side-effect that he called the "relaxed dissociated state."

Virtually all scientific investigators who have recently published in this area present similar opinions in their published writings, and largely attribute the antidepressant effects of ketamine to its pharmacological properties to alter the glutamate system, which in turn modulates other systems such as dopamine (aan het Rot et al., 2010; Bjerre & Fontenay, 2010; DiazGranados et al., 2010; Glue et al., 2011; Ibrahim et al., 2012; Liebrenz et al., 2007, 2009; Murroughet et al., 2011, 2012; Rasmussen et al., 2013; Rot et al., 2008; Zarate et al., 2006, 2012). This current biological theory proposes that, in addition to biochemical sub-types of depression caused by an "imbalance" of biogenic amines (serotonin, norepinephrine, and dopamine), there is also a separate sub-type of depression that biochemically mediates the same syndromic diagnosis of major depressive disorder due to an "imbalance" of glutamate (aan het Rot et al., 2010; Bjerre & Fontenay, 2010; Hashimoto, 2009; Ibrahim et al., 2012; Liebrenz et al., 2007; Machado-Vieira, Manji, & Zarate, 2009; Murrough et al., 2011; Rasmussen et al., 2013; Rot et al., 2008; Scolnick, Popik, & Trullas, 2009; Zarate et al., 2006, 2012).

There are complications with this theory. An existing NMDA receptor antagonist, memantine, was first developed in 1968 and has long been used as a neuro-protective agent and prescribed by some doctors for moderate-to-severe dementia. Like many other NMDA antagonists, memantine is a dissociative agent at above therapeutic doses (Morris & Wallach, 2014). It can even substitute for phencyclidine in rodent and primate drug discrimination studies (Parsons & Danysz, 1999). Although memantine has been associated in some studies with a modest decrease in the clinical deterioration of patients with moderate-to-severe dementia (Rossi, 2006), it has been reported as having only an insignificant positive effect on mood in the treated patients (Areosa, Sherriff, & McShane, 2005). There is still relatively little evidence of even a minimal effect on mild Alzheimer's disease (Schneider, Dagerman, Higgins, & McShane, 2011). Zarate and his

team have also reported that memantine does not relieve depression (Brown, 2007). The claim that memantine would be effective in Alzheimer's disease was rather surprising as it is well established that NMDA receptor blockade impairs memory rather than improving it (e.g., Collingridge, 1987). Ketamine users tend to report problems with their short-term memories rather than any improvement (Jansen, 2001; Morgan & Curran, 2012).

Another available glutamate-modulating agent, riluzole (Rilutetek), a drug that inhibits glutamate release, does somewhat improve depression but no better than conventional antidepressants and with the same time delay (Sanacora et al., 2007; Zarate et al., 2004, 2005). Riluzole was also researched in patients treated with ketamine in an attempt to sustain antidepressant effects. However, the studies failed to demonstrate any benefit over placebo in maintaining response to an IV ketamine infusion (aan het Rot et al., 2012; Brown, 2007; Ibrahim et al., 2012; Mathew et al., 2010).

A recent study using sophisticated proton magnetic resonance spectroscopy has specifically investigated ketamine's effects on glutamate brain levels in depressed patients but found no association between the antidepressant effects of ketamine and any significant changes in brain glutamate levels in both immediate (3 hours) and delayed (2 days) response to a ketamine administration (Valentine et al., 2011).

Undoubtedly, ketamine has many direct and/or indirect pharmacological effects on the human brain that may immediately improve the subject's mood. These effects are multifactorial. In addition to affecting the glutamate system (similarly to alcohol), ketamine affects the dopamine system (similarly to NRIs and amphetamines), GABA system (similarly to benzodiazepines), serotonin system (similarly to SSRIs), mu opioid system (similarly to opiates), cannabinoid system (similarly to THC), and nitric system (similarly to nitrous oxide or "laughing gas"). All of the above compounds have been shown to rapidly generate anti-anxiety and anti-depressant effects (especially when administered intravenously). The duration of their effects, however, has generally not much exceeded the pharmacological life of a particular compound and, it must be noted, its psychoactive metabolites which can be much longer.

Approximately one third of the ketamine subjects did not maintain a remission of depressive symptoms for longer than 24 hours post-infusion. Two thirds of the subjects did maintain a remission lasting from 2-5 days to 1-2 weeks. Why would remission last longer than one day? One possibility is some persistence of the NMDA-receptor active metabolites, with variations between people in the rate of metabolism due to genetic and life-style differences (Jansen, 2001). There are other psychiatric treatments where the persistence of metabolites, sometimes for many weeks, is accepted as central to the mechanism of action. The antipsychotic drug haloperidol is a good example, with the active metabolite lasting in the blood for many weeks. Thus ceasing to take haloperidol rarely results in an immediate relapse of psychosis.

However, it is also possible that the so-called "relaxed dissociated state" is not an unwanted side-effect, but is actually a cause of protracted remissions for psychological reasons. This may well prove to be the correct explanation. A recent study done by the Zarate group of investigators (Luckenbaugh et al., 2014) presented data from 108 treatment-resistant inpatients who met criteria for major depression or type I and II bipolar disorder and were given a sub-anesthetic ketamine infusion. The group examined whether dissociation experiences, measured by the Clinician-Administered Dissociative States Scale (CADSS), correlated with improvements in the Hamilton Depression Rating Scale (HDRS). The correlations' analysis indicated that there was a significant association between increased CADSS scores and improvement in HDRS scores, while none of the other analyzed parameters significantly correlated to HDRS change. The study concluded that those patients with more dissociation are also those in whom ketamine has a greater antidepressant efficacy, while the patients who did not show the dissociation did not have antidepressant efficacy in the post-infusion period.

This paper resonates with the earlier ketamine studies attributing a post-treatment remission of anxiety and depression to the quality of NOSC experience. It may be that one third of the experimental ketamine subjects had an alcohol-like euphoric affect and their remission thus lasted for no longer than 24 hours post-infusion. Another one third of the subjects had an MDMA-like empathogenic experience, and their remission lasted for 2-5 days post-infusion. The last one third of the patients had an OBE, and their remission lasted for 1-2 weeks and even longer. These odds are expected due to the fact that the standard 50 mg dose of ketamine used in the research subjects is located on the critical dosage

threshold between empathogenic and hallucinogenic responses, giving many subjects a 50% chance to have either an empathogenic or a hallucinogenic experience.

It seems that reducing the experiences of ketamine to just being due to biological causes may be doing injustice to their psychological, and even transpersonal, effects. The following clinical case supports the theory that psychological factors are important:

> W was a 59 year-old Caucasian female, with a past history of sexual abuse (between ages 11 and 17) and a life-long history of avoidant personality disorder (now re-classified as anxious personality disorder). She also developed scoliosis (a sideways curvature of the spine) during the growth spurt just before puberty and suffered from chronic pain since her mid-teens. In addition, she developed regular panic attacks, occurring 1-3 times a week, lasting from 10-20 minutes to several hours, since her late teens. W was raised as a Methodist, but converted to Hinduism at age 18, when she joined an ashram (a version of a contemporary monastery) in order to escape from her abuser (step-brother). W embraced a Yogini lifestyle and started practicing daily transcendental meditation, two times a day, 1 hour each sitting.
>
> At the age of 27, during an exceptionally long 10-day silent retreat, she spontaneously developed the Samadhi experience (ego-dissolving transcendental state of consciousness of mystical union with God) that lasted for several hours. W reported that after experiencing this state of "ecstatic bliss," her anxious personality, chronic pain, and recurrent panic attacks were "gone in a blink of an eye." Her remission lasted for 9 years until she was raped at the age of 36, which triggered a relapse of panic disorder, chronic pain disorder, and avoidant behavior. The rape also caused the onset of chronic depression.
>
> W continued meditating devotedly every single day and attended numerous silent retreats. However, she never had a mystical experience again. She had to start taking pharmaceuticals to control her chronic anxiety, depression, and pain, and she was treated with paroxetine, diazepam, and hydrocodone. The medications controlled her problems, but only partially. In addition, W slowly developed tolerance, which required a periodic upward adjustment of medication dose. By the time she requested ketamine treatment, she had to take daily 60 mg of paroxetine, 80 mg of diazepam, and 120 mg of hydrocodone. Despite high doses of three pharmaceuticals, she continued having chronic depression (her Back Depression Inventory [BDI] score was 29), chronic anxiety (her Beck Anxiety Inventory [BAI] was 36) and chronic pain (rated 7 on 0-10 scale).
>
> W considered undertaking KPP, after discovering a description of the EDT experience on Kolp's website, in which she recognized her spontaneous Samadhi experience. She had no difficulties to prepare herself for the experience, as she already practiced a vegan lifestyle, meditated and exercised daily, contemplated on the nature of the Self and God much of her waking time, and used screen time only occasionally. For the last 10 days of the preparation, she started practicing a juice fast in order to increase a chance of the EDT experience.
>
> The day before the administration of ketamine, W consulted her guru (a spiritual guide), who actively discouraged her from having the drug-induced EDT experience. She was apparently told that the "Creator cannot be experienced through a narcotic, you should instead double your meditation time." She accepted the guru's instruction and requested to have only 50 mg of ketamine, since W believed that this dose represented a medically-recommended dose that should be used as a therapeutic agent for the treatment of chronic "treatment-resistant" depression. Her therapist supported her wish, reminded W that she had a good chance of having the EDT experience due to her outstanding preparation, and instructed W "to close her eyes, start meditating, and surrender to whatever is to come." W followed this instruction, positioned herself in a Savasana ("corpse") pose, and then comfortably remained in the pose for the next 2 hours. Upon her return from the journey she shared this experience:
>
> > *As soon as I started breathing slowly and reciting my mantra my body started quickly relaxing and within 3 or 4 minutes the body became deeply relaxed and very comfortable. For the first time in the past 23 years the pain has disappeared. My mind was feeling very peaceful and calm … yet*

the mind remained fully awake and alert. Again, for the first time in the past 23 years, the sad mood and persistent anxiety have gone away. At that point I stopped meditating and started enjoying the profound feelings of empathy, compassion and love for myself. The whole experience was full of joy and peace … I only regret that I stopped meditating and did not transcend to the Soul Consciousness and then to the God Consciousness…

W maintained a symptom-free remission for 3.5 weeks and then developed a relapse of anxiety, followed by pain, and then depression. It was suggested that she undertake a second ketamine treatment. However, her spiritual guide persuaded her against it, pointing out that it may represent a drug-seeking behavior. The guru's advice was "keep meditating." At that point, W was started on phenelzine, 15 mg daily, with only a minimum response. After 4 weeks of treatment, the dose of phenelzine was increased to 30 mg daily, with a good response. W maintained a partial remission and her BDI score decreased to 17, the BAI score declined to 19, and her chronic pain level reduced to 3-4 on a scale of 10. She required two more adjustments of the phenelzine dose, to 45 mg 10 months later, and to 60 mg 17 months later. During her 2-year follow-up, W continued maintaining a steady remission: her BDI score further decreased to 14, the BAI score remained 19, and the chronic pain level became stable at 3.

As this case demonstrates, a spontaneous EDT experience can prolong the length of remission from depressive symptoms significantly longer than the best drug-induced empathogenic experience. Although all NOSCs may contribute to accelerated healing, it seems that the EDT experience may have the most healing potential.

The majority of Kolp's patients with chronic treatment-resistant depression (approximately 90%), who requested ketamine pharmacotherapy with a sub-psychedelic dose (50 mg IM), never had a trial with any MAOI antidepressants. Subsequently, Kolp began offering a trial with a MAOI antidepressant to all MAOI-naïve patients and recommended starting the trial on the day following the IM ketamine administration. Nearly 80% of the patients responded well, maintained a steady remission, and did not require a maintenance treatment with repeated IM administrations of ketamine.

Ketamine Addiction

The concerns of W's guru about drug-seeking behavior in some ketamine users do have merit, as ketamine can generate strong effects on mood (feelings), cognition (thinking), and perception (imagery) that make some people want to use it repeatedly. However, initially both the FDA and the DEA accepted the Parke-Davis testimonials and apparently agreed that ketamine has no addictive properties. It was subsequently discovered that ketamine is a substance with very significant dependence potential for multiple reasons (Jansen, 2001). In fact, the 68th edition of the *Physicians' Desk Reference* specifically warns physicians that prolonged use of ketamine may lead to tolerance and drug dependence (PDR Network, 2013). Kolp found that more than two thirds of his ketamine patients wanted to have another empathogenic experience the following day and nearly one third of the patients wished to promptly repeat a psychedelic experience.

Ketamine has been available to hospital staff since late 1960s, and persons working in this context were amongst the first ones to personally test the drug's empathogenic and psychedelic effects. The street use of ketamine hydrochloride solutions was first noted in San Francisco and Los Angeles circa 1971, while other forms of ketamine (powder and tablets) were first noticed on the street in 1974 (Ashley, 1978). Ketamine went under a variety of street names, including Special K and Vitamin K (Siegel, 1978).

One of the first reports describing the testimonials of non-prescription ketamine users came from Rumpf and his group of investigators (1969), whose subjects described ketamine hallucinations as "utopic," "fantastic," or "mysterious." Only one out of their 18 subjects considered the dream experiences normal and ordinary. The experience was termed pleasant by six subjects, unpleasant by eight, and neutral by four. Unexpectedly, Rumpf and colleagues reported that fully one third of the group (six subjects) had "true hallucinations" with the concomitant delusions that their dreams were not dreams, but, in point of fact, real events (Rumpf et al., 1969).

The first comprehensive study examining the patterns of ketamine addiction was done by Siegel (1978), who examined 23 subjects with recreational ketamine use. His sample included 13 injection users of ketamine and 10 intranasal ketamine users. Use of ketamine was primarily experimental or social in

nature, and the drug was viewed by users to be a potent yet safe hallucinogen with a short duration of action and few if any adverse effects. Ketamine users tended to titrate their use in order to achieve the desired effects of stimulation, dissociation, visual hallucinations, and transcendental experiences (Siegel, 1978). When asked to rank all drugs in terms of general recreational preference, Siegel reported that intranasal users ranked cocaine first, while injection users ranked LSD first. The users consistently described ketamine in the following ways:

- Ketamine was perceived by users to be a safe, non-toxic, potent hallucinogen with a short duration of action and few adverse reactions.
- Ketamine was perceived by most users as the only hallucinogen that did not produce anxiety or fear reactions.
- Ketamine was considered to have unique euphoric-hallucinogenic properties that enabled a user to experience, with varying dosages, effects similar to either cocaine, amyl nitrite, phencyclidine, or LSD.

Ketamine users repeatedly sought and experienced the following desirable effects: floating sensations and dissociation (87%), stimulation (83%), hallucinations (78%), increased cognitive or mental associations (74%), euphoria (26%), and transcendental or religious experiences (17%). Despite the widespread beliefs among users about the lack of adverse reactions, a number of untoward effects were also reported, including ataxia (100%), slurring of speech (70%), dizziness (61%), mental confusion (35%), hyperexcitability (26%), unpleasant imagery (26%), blurring of vision (17%), negative hallucinations, or the inability to see things that were really there (17%), decreased sociability (17%), anxiety (13%), nausea (13%), insomnia (13%), and decreased sexual motivation (9%).

Siegel (1978) documented the specific long term effects, both positive and negative, resulting from ketamine use. Some ketamine users described a lasting elevation of mood (43%), deeper insights into self and others (35%) and positive changes in attitudes and personality (17%). Other ketamine users reported undesired long term effects including flashbacks (57%), attentional dysfunction (22%), and decreased sociability (9%). Overall, long-term effects appeared equally divided between positive and negative experiences.

Ketamine was further popularized during the 1970s by John Lilly, and to a lesser extent by astrologer Marcia Moore, who wrote books on the subject of self-use of ketamine. Lilly published a book entitled *The Scientist* (1978) and Moore (together with her husband, Dr. Alltounian) published a book called *Journeys into the Bright World* (1978). Both books documented the unusual phenomenology of ketamine intoxication and prompted others to experiment with ketamine. Subsequently, many ketamine users in the "first wave" preferred ketamine for its psychedelic properties and administered it via IM self-injections.

The ketamine scene began changing during the late 1980s to early 1990s when lower doses of ketamine in pill and powder form, for intransal use, became more prevalent due to its empathogenic and stimulant effects at lower doses (Tori, 1996; NDIC Bulletin, 2004). Ketamine began appearing on the club, underground party, and rave scenes, being used together with or instead of ecstasy (MDMA), cocaine, and amphtamines. By the mid-1990s, ketamine had entered mainstream dance culture, and it remains a popular dance drug today (e.g., Joe-Laidler & Hunt, 2008).

Eventually, the U.S. Drug Enforcement Agency (DEA) became alarmed by this development and changed ketamine's schedule in August of 1999, making it a controlled substance and moving the drug to Schedule III of the Controlled Substances Act of 1970. Other countries have also done so, most recently India which had been a major source for the European market. India is now being replaced by China as the source. In 2000 the Hong Kong government placed ketamine in Schedule 1, a drastic measure in response to the recent rise in ketamine prevalence in East Asia.

As previously noted, the Russian government moved ketamine from Schedule III into Schedule II in 2002 after ketamine became popular with Muscovite teenagers. In 2005, Canada re-classified ketamine as a Schedule I narcotic. The United Kingdom has moved ketamine from Class C to Class B in June of 2014, and controls were also tightened in New Zealand. These more recent changes were partly driven by the reports of binge non-medical ketamine use being linked with damage to the urinary system in some users. In addition, ketamine is in Category 3 under Mexico's General Health Law. However, generic ketamine is still easily obtained in a "veteranaria farmacia" as "ketamina" for $15 to $20 a gram. According to a DEA report from 2004, over 80%

of ketamine seized in the United States at that time, ten years ago, was of Mexican origin (NDIC Bulletin, 2004).

Unlike phencyclidine, ketamine production is a complex and time-consuming process, making clandestine manufacturing of ketamine impractical. Meanwhile, ketamine is produced commercially in a number of countries, including (for example) the United States, Mexico, Columbia, China, India, Germany, and Belgium, where it may be diverted from legitimate sources. There have also been reports of industrial-scale illicit ketamine manufacture in China (UN Office on Drugs and Crime, 2010).

Ketamine's use as a recreational drug has been rising over the last 30 years (Copeland & Dillon, 2005; Dillon & Degenhardt, 2001; Jansen, 2000; Moore & Measham, 2008). Travis (2005) reported that ketamine was one of the six most common drugs for sale in UK cities. Stirling and colleagues (2008) published an update on recreational drug use in the United Kingdom and reported that 4% of the young adults in the study had tried ketamine at least once. Dillon, Copeland, and Jansen (2003) reported that about 1 in 3 Australian respondents in a study of a drug user culture acknowledged the use of ketamine in the previous 12 months. The 2006 National Survey on Drug Use and Health (NSDUH) reported that in the United States an estimated 2,300,000 persons aged 12 and older had used ketamine in their lifetime, and 203,000 were past year users (NSDUH Report, 2006).

There is a substantial popular literature describing ketamine dependence (e.g., Lilly, 1978; Sputz, 1989; Turner, 1994). Ketamine recurrent binges can be sustained for many days and even several weeks. The medical literature has documented the same and the number of case studies is mounting (Ahmed & Petchkovsky, 1980; Hurt & Ritchie, 1994; Jansen, 1990a, 1990b, 2000, 2001; Kamaya & Krishna, 1987; Moore & Bostwick, 1999; Morgan & Curran, 2012; Soyka, Kripinsky, & Volki, 1993). The evidence from animal studies indicates that ketamine can form a dependence syndrome (Beardsley & Balster, 1987). The multiple problems related to dependence on ketamine, including education, relationships, employment, finances, and involvement in crime, have also been documented (Lim, 2003).

In his private practice, Kolp has been handling ketamine as a Schedule II substance and has been repeatedly warning all patients that ketamine should never be used except under the direct supervision of a licensed physician. Instead of a ketamine maintenance treatment, Kolp encourages all MAOI-naïve patients to have a trial with MAOIs first, prior to commencing recurrent administrations of ketamine. To those patients who do not accept a trial with MAOI, or who failed it, Kolp offers a maintenance treatment with IM ketamine. However, he prefers limiting the frequency of ketamine IM administration to once every 4-6 weeks and never more frequently than once every 2 weeks. Kolp does not utilize oral, sublingual, or intranasal ketamine maintenance treatment for his patients in order to minimize the potential for ketamine abuse and dependence. The procedural parenteral approach (administering IM and IV ketamine in the office) would reduce the abuse and dependence potential by strictly controlling access to ketamine. In contrast, dispensing the drug to the patients (in-home oral, sublingual, and intranasal self-administration) would likely increase the abuse and dependence potential by increasing access to ketamine, and normalizing the use rather than this being a "special event."

Potential Side-Effects of Ketamine Long-Term Treatment

The previously presented data on ketamine's safety profile has been established for episodic and/or time-limited use of ketamine. Meanwhile, the side-effects of acute and intermittent uses of a chemical substance and side-effects of the chronic use of the same compound may have two entirely different profiles. Once ketamine (and other similar glutamergic compounds) are sanctioned for use as oral anti-depressants, tens of millions of patients may start using this class of chemical compunds for an extended period of time. There may be value in comparing both the acute and chronic use of ketamine with another compound described as having some similar glutamergic properties.

Ethanol, similar to ketamine, has the capacity to block glutamate effects at the NMDA receptor, which contributes to ethanol's acute behavioral effects and to the natural history and neuropathology of alcoholism (Tsai, Gastfriend, & Coyle, 1995). Ethanol decreases the NMDA-stimulated ion currents across the range of ethanol concentrations (from 5 to 100 mmol/L) that has been associated with human ethanol intoxication (Lovinger, White, & Weight, 1989; Nakanishi, 1992; Simson et al., 1991). Meanwhile, chronic long-term ethanol consumption increases the levels of NMDA receptors, up-regulates NMDA receptor-

related binding, and produces cross-tolerance with other noncompetitive NMDA antagonists (Danysz, Jankowska, Glazewski, & Kostowski, 1992; Fidecka & Langwinski, 1989; Grant, Valverius, Hudspith, & Tabakoff, 1990; Iorio, Reinlib, Tabakoff, & Hoffman, 1992; Trevisan et al., 1994).

This increased NMDA receptor function produced by chronic long-term ethanol consumption contributes to alcohol withdrawal seizures (Grant et al., 1990) and ethanol neurotoxic effects (Chandler et al., 1993). The NMDA antagonists ketamine and phencyclidine substitute for ethanol in preclinical drug discrimination paradigms (Grant & Colombo, 1993; Grant, Knisely, Tabakoff, Barrett, & Balster, 1991). This biochemical data may allow extrapolation of the effects of chronic long-term ethanol consumption to some possibly analogous effects of long-term chronic administration of ketamine and other related NMDA antagonist compounds.

Ethanol has well-known anxiolytic and antidepressant effects with a robust onset of action and good anti-shock (neuro-protective) qualities when used sporadically. It usually only has a few serious side-effects when used episodically. The side-effects of acute ethanol use, however, are very different than the side-effects of chronic use. Ethanol, a known NMDA antagonist, is notorious for its ability to trigger apoptotic neurodegeneration when used chronically (Hoffman, Rabe, Moses, & Tabakoff, 1989) and is a leading cause of dementia (Moriyama, Mimura, Kato, & Kashima, 2006).

A laboratory study conducted on primates suggested that chronic use of ketamine may induce neuronal cell death that is both apoptotic and necrotic in nature (Slikker et al., 2007). Other experimental data have confirmed this earlier study and documented that chronic ketamine exposure might produce irreversible deficits in brain functions due to neurotoxic effects, involving the activation of apoptotic pathways in the prefrontal cortex (Sun et al., 2014). A recent epidemiological study conducted on frequent and infrequent ketamine users reported that frequent ketamine use is associated with impairments in working memory, episodic memory, and aspects of executive function as well as reduced psychological wellbeing (Morgan, Muetzelfeldt, & Curran, 2009). The preliminary data are suggestive that once ketamine and other similar glutamergic compounds become available on the market as oral anti-depressants, chronic long-term use might cause neurodegenerative changes in the brain of some patients.

The Future of Ketamine Psychotherapy from a Pharmacological Perspective

Although there is currently a lack of scientific data supporting a glutamate "imbalance" as a primary pathophysiological cause of major depression, there is a very short duration of post-ketamine remission of depression, and there are questions regarding the long-term adverse effects of chronic use of ketamine, there is excitement in the psychiatric research community about the discovery of a new class of antidepressants with a mechanism that may be beyond the effects of biogenic amine neurotransmission.

Professor Preskorn (2012) of Kansas University School of Medicine, who has been the principal investigator on over 250 clinical trials including drug development studies of all antidepressants marketed in the United States in the last 25 years (www.preskorn.com), pointed out that all of the existing antidepressants are variations on the pharmacology of amphetamine, iproniazid (MAOI), and imipramine (TCA) and predicted that ketamine and related drugs could revolutionize psychiatry. Yale professors Ronald Duman and George Aghajanian, in a recent 2012 review of the ketamine research in *Science*, stated that the emerging ketamine treatment is the most important psychiatric discovery in recent times.

Nevertheless, it is very unlikely that ketamine will be developed for a mass market. It is an old drug that has long been off patent, so it is not currently profitable for drug manufacturers. The issue of some risk to the kidneys and bladder among some non-medical users is not going away and affects perceptions, although the quantities involved and the circumstances for these people may differ markedly from its use for antidepressant, psychedelic, and other treatment regimens, and the risk in the latter situations will likely be minimal. Furthermore, its reputation as an abused hallucinogen may now be too firmly embedded in the public awareness for any kind of marketing campaign of the sort commonly associated with antidepressants with billions of dollars at stake.

In addition, the accepted model for all available antidepressants is oral administration. Even ECT treatment involves both an anaesthetic (sometimes ketamine is used for this, and poses an important confounding variable in some ECT studies) along with the production of seizures with electricity. The intravenous and intramuscular routes of antidepressant

administration will severely limit the market size. The profit to be made from ketamine by the pharmaceutical industry from its use as an antidepressant thus appears to be somewhat limited. An aim of the present ketamine campaign will be to encourage research and development of similar NMDA receptor antagonist compounds that may be more profitable. Ketamine on its own has eight presently known metabolites, including esketamine, arketamine, bromoketamine, deschloroketamine, ethketamine, fluoroketamine, methoxetamine and methoxyketamine. Meanwhile, the entire arylcyclohexylamines group of presently known chemical compounds has nearly 60 various compounds. Reportedly, at least 30 other unscheduled analogs have been produced by clandestine sources.

As of July 2014, Johnson & Johnson is developing a nasal spray formulation of esketamine for the management of treatment-resistant depression (Wijesinghe, 2014). Esketamine (a.k.a. (S)-ketamine or S(+)-ketamine) is the S(+) enantiomer of ketamine and twice as potent as racemic ketamine. A Phase 1 clinical trial of intranasal esketamine is sponsored by a Johnson & Johnson subsidiary, Janssen Pharmaceutical Research & Development, LLC. This company is conducting a clinical trial with 58 participants in Belgium; the purpose of this study is to assess the efficacy and dose response of intranasal esketamine (14 mg, 28 mg, 56 mg, and 84 mg) compared with placebo (clinicaltrials.gov/show/NCT01998958).

Another privately held biopharmaceutical company, Naurex Inc., has recently announced that it has successfully completed a Phase 2b clinical study of GLYX-13, the company's lead compound (www.naurex.com). The FDA has already granted Fast Track Designation to the research and development of this compound. The company also reported that it initiated a Phase 2a study of another orally active agent, NRX-1074, after collecting positive results from a recently completed Phase 1 study of the NRX-1074 drug. Both compounds are NMDA receptor antagonists. However, their specifics are unknown. Krystal, who may be one of the most powerful figures today in biological psychiatry, has endorsed research and development of both compounds, and Preskorn is a study investigator (www.naurex.com).

Cerecor Inc., a Maryland-based biopharmaceutical company, is also in the process of developing a new antidepressant drug, CERC-301 (formerly known as MK-0657), as a therapy for TRD. The drug is a selective NMDA receptor antagonist and an orally-active compound (Ibrahim et al., 2012). The company has initiated phase II clinical trials in November of 2013 and this study has received Fast Track Designation from the FDA for TRD (www.cerecor.com).

AstraZeneca, PLC (AZN) is studying another NMDA receptor antagonist, lanicemine (Wijesinghe, 2014). Lanicemine was originally developed as a neuroprotective agent and then was redeveloped as an antidepressant following the report of Zarate and colleagues (2012), who documented that lanicemine has potent antidepressant effects similar to ketamine. However, the drug is claimed to have little or no psychotomimetic side effects (Zarate et al., 2012).

Although ketamine itself will probably not become the next generation of anti-depressants, it seems that numerous other members of the arylcyclohexylamines class will be presented for this purpose, and probably also presented as the next generation of anti-anxiety drugs, mood-stabilizers, and procognitive agents. Their impact on the urinary system will need to be assessed where long-term daily use is planned. It remains to be seen whether the next generation of glutamate-antagonist based pharmaceuticals will result in a growth of addiction to those which are psychoactive arylcyclohexylamines.

In addition to this flurry of activity to develop psycho-pharmacological applications of ketamine, especially in ways that can yield profits, there remains its psychological and transpersonal healing potential. Our position is that these offer its greatest likelihood of benefit, rather than through ketamine's biological application.

Conclusion

Ketamine is a potent substance that offers much promise for alleviating suffering due to mental health issues, but it also poses considerable danger when it is misused. As a psychiatric medication, ketamine offers a wide range of applications, from mild doses alleviating depression (at least in the short-term) to psychedelic dosages offering the possibility of transpersonal healing. The fact that ketamine is the only psychedelic that can legally be prescribed in the United States makes it unique at this time, and we encourage its responsible use within medical contexts for providing access to deep and profound healing experiences that may be difficult, if not impossible, for many to achieve without the aid of such a substance.

We hope that ketamine will remain legally available for clinical applications and scientific research, including for the field of psychedelic psychotherapy. The current interest in ketamine may eventually bring psychedelic psychotherapy somewhat closer to the mainstream of psychiatry and psychology. Those dismissive of its spiritual component, who are inclined to consider this as "flakey," should bear in mind that the most successful and cost-effective treatment for alcohol dependence remains the 12-step programs, such as Alcoholics Anonymous (The Fellowship; Alcoholics Anonymous World Services, 1984), and of course the spiritual component lies at the very heart of this approach (Corrington, 1989; Nathan, 1986). Spirituality retains a place in contemporary psychiatry. It is not so long ago that the Spirituality Special Interest Group became one of the nine Special Interest Groups at the Royal College of Psychiatry in London, and interest continues to grow. It would be difficult to argue that all of these psychiatrists are part of a lunatic fringe.

The United States is a country in which the overwhelming majority of the population has some spiritual beliefs. When one considers the high morbidity and mortality from disorders such as alcohol dependence and depression, it seems foolish to neglect all of the opportunities for treatment which this circumstance may offer. From a contemporary perspective, KPP is less drastic than some of its alternatives, such as ECT used for TRD and for which ketamine is sometimes used as an anaesthetic (and may even be the source of much of ECT's purported effectiveness). It may be time for a cultural shift in perceptions. With billions of dollars at stake, it is understandable that some vested interests may directly and/or indirectly lobby to oppose any shift away from the culture of taking daily tablets (or perhaps nasal sprays) and the use of ECT as the ultimate psychiatric treatment. However, if protocols develop which combine innovative methods, such as KPP with ongoing maintenance alongside conventional medicines as "standard practice," some of the profit-based opposition may eventually lessen. Likewise, opposition from both conservative factions that might oppose any substance that can be seen as generating a "high," as well as by more spiritually liberal factions that might denigrate such substances as less valid than using so-called "natural" approaches (e.g., meditation), would have to be confronted in the face of the tremendous suffering that KPP could alleviate.

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Eli Kolp, MD, Eli Kolp, M.D., was born and educated in the former Soviet Union, where he completed medical school in 1973 and residency training in psychiatry in 1978. Dr. Kolp immigrated to the United States in 1981 and completed second residency training in psychiatry in 1987 at the University of Texas in Houston. In 1988, Dr. Kolp moved to Tampa, where he joined the faculty of the Department of Psychiatry at the USF College of Medicine and became a Diplomate of the American Board of Psychiatry and Neurology.

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