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# **Ketamine-Enhanced Psychotherapy: Preliminary Clinical Observations on its Effects in Treating Death Anxiety**

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Ketamine, a dissociative anesthetic commonly used by US physicians, has recently been shown to be a powerful anti-depressant and is also capable of eliciting transpersonal experiences that can be transformative. Although currently approved in the US only for use as an anesthetic, physicians there can legally prescribe it off-label to treat various psychological/psychiatric problems and it has been used for these non-anesthetic purposes in Argentina, Iran, Mexico, Russia, and the UK, as well as in the US. The literature on using ketamine psychotherapeutically is reviewed and two case studies using ketamine-enhanced psychotherapy (KEP) for treating death anxiety in terminally-ill people are reported. The potential importance of beginning formal research on using KEP during end-of-life for those suffering death anxiety is emphasized.

## **Introduction**

**T**he experiential phenomena associated with death remain unknown. Meanwhile, we all know that it is the only certainty in life. Everything that lives dies—with no exception. However, human beings alone are known to be burdened with the cognitive capacity to be aware of our own inevitable mortality and to fear what may come afterwards. A central drive of all human beings is a self-preservation instinct. Combining this instinct with the awareness that death is inevitable creates in some of us a paralyzing terror of non-existence, which we struggle to overcome through both conscious efforts and unconscious defense mechanisms. Our death anxiety may be exponentially intensified during the end-stage of any terminal illness when we face death without refuge. Therefore, it may become necessary to help some dying people manage death anxiety in such a way that it resolves existential and other fears related to the end-of-life issues. Psychedelic psychotherapy—combined with

other conventional treatment approaches—may be a powerful technique to deal with this challenge, and it may also be a useful standalone treatment for patients who have had little to no success with more conventional approaches.

Numerous clinical research studies of terminally-ill patients (e.g., with end-stage cancer) treated with psychedelic compounds (i.e., primarily lysergic acid diethylamide [LSD]) were performed from the late 1950s to the early 1970s and sometimes demonstrated remarkably impressive treatment outcomes (e.g., Pahnke, 1968, 1969; Pahnke, Kurland, Goodman, & Richards, 1969; Pahnke, McCabe, Olsson, Unger, & Kurland, 1969; Pahnke, Kurland, Unger, Savage, & Grof, 1970; Pahnke, Kurland, Unger, Savage, Wolf, & Goodman, 1970; Richards, Grof, Goodman, & Kurland, 1972; Watts, 1973; Richards, Rhead, DiLeo, Yensen, & Kurland, 1977; Richards, Rhead, DiLeo, Grof, Goodman, DiLeo et al., 1979; Grinspoon &

Bakalar, 1979; Richards, 1979/1980; Grof, 1980; Yensen & Dryer, 1993/1994; Grob, 1998, 2002; Walsh & Grob, 2005). Kast pioneered pain treatment with LSD in patients with terminal cancer by discovering that low dose LSD (100 micrograms) brought greater analgesia than more widely used medication (such as Dilaudid [hydromorphone] and Demerol [meperidine]) and that these superior effects lasted for several days as opposed to several hours; in addition, he and colleagues documented diminished fear of death and significant reduction of depressive symptoms (Kast, 1962, 1966a, 1966b; Kast & Collins, 1964). Another investigator replicated Kast's findings by treating dying patients with LSD (Cohen, 1965).

The most comprehensive research on LSD-assisted psychotherapy on patients with terminal cancer was done by Pahnke at the Maryland Psychiatric Research Institute from 1965 through the early 1970s; these studies asserted that the most powerful results from treatment were induced by transpersonal (e.g., spiritual, mystical, or peak) experiences (Pahnke, 1968, 1969; Pahnke et al., 1969; Pahnke, McCabe et al., 1969; Pahnke et al., 1970; Pahnke, Kurland et al., 1970). Findings from these studies indicated that two-thirds of the LSD treated cancer patients had significant improvement with reductions in pain, depression, and fear of death.

The final study of that era was done by Grof, who used LSD-assisted psychotherapy for treatment of 60 patients with terminal cancer (Grof, Goodman, Richards & Kurland, 1973). The study measured levels of anxiety and depression, and the amount of narcotics before and after LSD treatment. The measures also included the MMPI and Attitude to Death tests. Grof reported that 29 percent of his treated patients showed dramatic improvement, with an additional 41.9 percent of patients showing moderate improvement.

The medical use of psychedelic substances was subsequently rejected in the US and most other Western countries after the onset of the "war on drugs." This war emphasized psychedelics' potential for harm (Cornwell & Linders, 2002) while overlooking their significant promise, thus potentially extracting a huge cost on society as a whole (Miron, 2004). One of the consequences of the suppression of psychedelic research (with the exception of ketamine) was an unjustified minimization of their potential therapeutic value, even though there is voluminous research literature supporting both the therapeutic efficacy and safety of psychedelic drugs when

used by professionals for treating numerous addictive disorders and mental health problems (Friedman, 2006).

However, this prohibition on research has changed recently with approval of several US studies of psychedelic psychotherapy for treating psychological/psychiatric problems, including those related to terminal illnesses (Friedman, 2006). One such study at Harbor-UCLA Medical Center, for treatment of existential anxiety in end-stage cancer patients, started in 2004 and was the first known legally-conducted study on this topic after the decades of prohibition; this study utilizes a psychedelic agent psilocybin (4-phosphoryloxy-N,N-dimethyl-tryptamine) and was developed and funded by the Heffter Research Institute (see [www.canceranxiestudy.org](http://www.canceranxiestudy.org)). Another study, pending IRB approval at the Mount Sinai Comprehensive Cancer Center in Miami, was developed and funded by the Multidisciplinary Association for Psychedelic Studies (see [www.MAPS.org](http://www.MAPS.org)) to evaluate the effectiveness of psilocybin-assisted psychotherapy for reduction of distress in patients with advanced melanoma (personal communication, Sameet Kumar, April 4, 2007).

Our paper focuses on the clinical potential of another psychedelic drug, ketamine hydrochloride (ketamine), which can legally be used by US physicians to treat psychological/psychiatric problems including anxieties in dying patients. We present two case studies on the use of ketamine-enhanced psychotherapy (KEP) for anticipated grief resolution (AGR) in patients with end-of-life issues. The first case documents a successful resolution of anticipated grief outcome after KEP, while the second case illustrates some of KEP's limitations.

### **Overview of Ketamine**

The medication ketamine [2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] has many effects in the brain, but there is now broad agreement that a key action is its noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor that modulates the neurotransmitter glutamate. It produces extremely effective analgesia and, for more than 30 years, has been commonly used in clinics and hospitals as an anesthetic for children, adults, and the elderly due to its rapid onset and short duration of action. Also due to its exceptional analgesic properties, ketamine is widely used at sub-anesthetic doses for management of breakthrough pain in patients with acute and chronic pain, for treatment of

neuropathic pain disorder, ischemic limb pain disorder, refractory cancer pain, as an adjunct to standard opioid therapy, and as a pediatric sedation tool for use with acutely injured children (Petrack, Marx, & Wright, 1996; Carr, Goudas, Denman, Brookoff, Staats, Brennen et al., 2004; Ellis, Husain, Saetta, & Walker, 2004; Green & Krauss, 2004; Howes, 2004; McGlone, Howes, & Joshi, 2004; Rakhee & Milap, 2005; Visser & Schug, 2006).

Ketamine use is devoid of life-threatening side-effects and several instances of unintentional administration of overdoses of ketamine—up to ten times that usually required—have been followed by prolonged but complete recovery (Physician Desk Reference, Product Information). All previous clinical studies have both established its greater safety (e.g., Green & Krauss, 2004; White, Way, & Trevor, 1982) and failed to detect any long-term impairment as a consequence of its use (e.g., Siegel, 1978). In fact, there is a plethora of recent studies investigating the possibility of damage related to ketamine with normal, pathological (e.g., patients with schizophrenia), and ketamine-abusing volunteers. The majority of these studies suggest that ketamine can be safely used for treatment of various psychological/psychiatric problems (Morgan, Mofeez, Brandner, Bromley, & Curran, 2004; Karst, Wiese, Emrich, & Schneider, 2005; Cho, D'Souza, Gueorgiueva, Perry, Madonick, Karper et al., 2005; Parwani, Weiler, Blaxton, Warfel, Hardin, Frey et al., 2005; Holcomb, Medoff, Cullen, & Taminga, 2005; Morgan, Rossell, Pepper, Smart, Blackburn, Brandner et al., 2006).

In addition, more than 7,000 published reports describe ketamine's high level of effectiveness in a variety of other clinical applications (Shapiro, Wyte, & Harris, 1972; Reich & Silvay, 1989; Ross & Fochtman, 1995; Dachs & Innes, 1997; Bauman, Kish, Baumann, & Politis, 1999; Green & Krauss, 2000; Ersek, 2004). According to several reports, ketamine in fact prevents brain damage from head trauma, strokes, heart attacks, epileptic seizures, low oxygen levels, and low blood-sugar levels (Shapiro et al., 1972; Weiss, Goldberg, & Choi, 1986; Rothman, Thurston, Hauhart, Clark, & Solomon, 1987; Shapira, Lam, Eng, Laohaprasit, & Michel, 1994; Hirota & Lambert, 1996).

The most extensive studies of the biochemical aspects of ketamine have been done by a US researcher, Krystal, who has been focusing on its effects on perceptual and cognitive functioning (Krystal, Karper, Seibyl, Freeman, Delaney, Bremner et al., 1994). His

group of investigators also completed clinical research studying the effect of ketamine's NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients (Krystal, Petrakis, Limoncelli, Webb, Gueorgueva, D'Souza et al., 2003). In addition, Krystal's team reported antidepressant effects of ketamine (Berman, Cappiello, Anand, Oren, Heninger, Charney et al., 2000). These antidepressant effects of ketamine have been recently confirmed by a group of government investigators at the National Institute of Mental Health (Zarate, Singh, Carlson, Brutsche, Ameli, Luckenbaugh et al., 2006), documenting a dramatic improvement in patients' mood in a matter of hours among a sample of eighteen treatment-resistant patients diagnosed with major depressive disorder. It is noted that these newly documented powerful antidepressant effects of ketamine are of great potential importance.

One of us (Krupitsky) has collaborated in researching the psychopharmacology of ketamine at Yale with Krystal (Krupitsky, Burakov, Romanova, Grinenko, Fletcher, Petrakis et al., 2001; Krystal, Petrakis, Krupitsky, Schütz, Trevisan, & D'Souza, 2003). Krupitsky also conducted independent studies of ketamine psychopharmacology and biochemistry (e.g., Krupitsky, Grinenko, Karandashova, Berkaliyev, Moshkov, & Borodkin, 1990) at the Center for Research in Addiction and Psychopharmacology in St. Petersburg, Russia, researching the effects of ketamine administration on metabolism of biogenic amines.

Although there are both widespread medical usages of ketamine as an anesthetic and significant ongoing research on many other applications of ketamine within the US, we know of no current studies examining this medication's usefulness for the treatment of psychological/psychiatric problems. We are especially concerned that its potential for treating anxieties related to end-of-life issues has been ignored. This may be due to the fact that ketamine is seen as a potent psychedelic agent. It reliably causes powerful alterations in consciousness (e.g., in mood, perception, and thought) that naturally occur only during dreaming, memory flashbacks, psychoses, and mystical experiences (Rumpf, Pedick, Teuteberg, Munchhoff, & Nolte, 1969; Grinspoon & Bakalar, 1979; Grinspoon, 1986), and this is deemed undesirable in the suppressive climate related to the war on drugs. Nevertheless, given that many research studies on the clinical effectiveness of psychedelics are now resuming in the US (Friedman,

2006), it is an opportune time to conduct further studies on the effectiveness of ketamine therapy. One fact that makes ketamine especially appealing as a psychedelic drug for research and clinical practice is that it is currently legal for medical practitioners to use in the US now (i.e., it can be legally prescribed “off-label”<sup>1</sup> by physicians for psychotherapeutic purposes). This legal status may greatly facilitate the process of getting approval for ketamine’s use in formal clinical research, unlike the case with other psychedelics that require surmounting numerous bureaucratic hurdles. In addition, there is one other advantage to ketamine over similar substances, namely its effects are of short duration and can be managed within the customary timeframe of most psychological/psychiatric sessions (i.e., in approximately one hour), so it can fit into current service delivery systems.

It is also important to emphasize that there has been an increase of ketamine abuse (Sputz, 1989; Jansen, 1993). When ketamine is used in uncontrolled settings recreationally, it can lead to significant medical problems, including excessive sedation and respiratory depression—especially if combined with depressants like alcohol, benzodiazepines, or gamma hydroxybutyrate (Ricuarte, 2005). Frivolous use of ketamine may also cause impairment of episodic memory and attentional functioning (Morgan, Monaghan, & Curran, 2004). Therefore, we emphasize that ketamine should never be used in any way other than for research or clinical applications under the supervision of qualified and licensed professionals.

### **Transpersonal Effects of Ketamine**

There is no consensual opinion regarding how psychedelic substances might work beneficially within clinical settings. Most of the researchers view the active mechanisms of psychedelic substances solely from a biochemical perspective. Ketamine is often considered a “psychomimetic” (i.e., causing effects mimicking psychoses), prompting some US investigators to use ketamine-induced phenomena as a model for studying psychoses in experimental research (e.g., Krystal et al., 1994). In this model, the psychedelic effects of ketamine are seen as undesirable rather than as a potential therapeutic mechanism.

Contrary to this view, we propose that ketamine’s powerful psychotherapeutic effect is possibly due to its psychedelic-including transpersonal experience generating-properties, as it frequently induces in

sub-anesthetic doses feelings of ego dissolution and loss of identity, emotionally intense visions, visits to mythological realms of consciousness, vivid dreams and memories of possible past incarnations, experience of the psychological death and rebirth of the ego, and feelings of cosmic unity with humanity, nature, the universe, and God. These observable facts were initially described as “emergence phenomena” (White et al., 1982) and clearly depict a psychedelic experience. These non-ordinary states of consciousness offer an additional or alternative mechanism of ketamine’s effects over and above purely biological explanations. One of us (Friedman, 2006) previously speculated that psychedelic drugs such as ketamine are specifically useful due to their transpersonal, rather than solely neurobiological, effects. This is also congruent with the conclusions of numerous researchers that spiritual factors are crucial in treating many psychological problems, such as is frequently discussed for alcoholism (e.g., Robinson, Brower, & Kurtz, 2003; Amodia, Cano, & Eliason, 2005).

Grof (1980) has developed a comprehensive theory of psychedelic psychotherapy from this perspective. He concluded that psychedelic substances facilitate therapeutic experiences of symbolic death and rebirth of the ego, allowing clients to work through deep traumatic fixations in their unconscious. Grof successfully applied this specific transpersonal psychotherapeutic approach to more than 750 patients. He explicitly discouraged his clients from analyzing their psychological problems and instead assisted them in transcending their inflexible maladaptive patterns, placing a strong emphasis on their transpersonal growth potential. Although Grof primarily used LSD as a psychotherapeutic agent, he acknowledged that ketamine holds great promise due to its “affinity for positive dynamic systems” (p. 214). He stated that the psychoactive effect of ketamine is so powerful that “it catapults the patient beyond the point of impasse from the previous LSD session, and can make it possible for him or her to reach the better level of integration” (p. 214).

There is another specific advantage that ketamine has over other psychedelic substances (i.e., in addition to it being legally available through off-label prescription and of short duration), namely its well-documented ability to reliably replicate near-death experience [NDE] (Domino, Chodoff, & Corssen, 1965; Stafford & Golightly, 1967; Rumpf et al., 1969; Collier, 1972; Siegel, 1978, 1980, 1981; Grinspoon & Bakalar, 1979; White et al., 1982;



Ghoniem, Hinrichs, Mewaldt, & Peterson, 1985; Lilly, 1988; Sputz, 1989; Kungurtsev, 1991). One of us (Jansen) analyzed similarities between ketamine-induced transpersonal experience and NDEs in a series of studies, concluding that the intramuscular administration of 150-200 mg of ketamine can reliably reproduce all of the features commonly associated with NDEs (Jansen, 1989a, 1989b, 1990, 1991, 1997, 2001).

The NDE is an altered state of consciousness usually reported by a person who has experienced so-called clinical death and has then revived. This is an episode split off from the patient's usual life and marked by unusually intense dream-like events. Typical characteristics of an NDE include a sense that one is truly dead, a perception of separation from the body or out-of-body experience, a sense that what is experienced is real, ineffability or a sense that the experience is beyond words and cannot be described using language, and transcendence of time and space (Ring, 1980, 1984; Greyson, 1983). Some people believe that they were actually "in death," reporting that after "dying" they left their body and floated away, became enveloped in a dark tunnel, and then entered a soothing light; later when they "came back to life," these individuals are reportedly sometimes able to recall the events that occurred when they were "dead" (Grof & Halifax, 1977; Osis & Haraldsson, 1977).

Greyson reported approximately 70 percent of NDEs are accompanied by feelings of calm and peace, while about 30 percent of NDEs are very frightening (Greyson, 1983; Greyson & Stevenson, 1980). These studies suggest that past memories are often organized into a life review and patients often report that, during the NDE episode, their entire past flashes before them. Transcendent mystical states are also common, with visions that include meaningful figures (e.g., parents, teachers, partners, friends, etc.) who may be already dead or still alive at the time, as well as archetypal images (e.g., of angels, Buddha, Christ, Krishna, or any other gods and goddesses) representing patients' belief system. The experience of God is often reported as an ocean of luminescent white light. After effects of NDEs include: decreased fear of death accompanied by increased appreciation of life, increased spirituality and concern for others, and decreased materialism and competitiveness. Two of us (Jansen and Kolp) had personal NDEs from natural causes, as well as transpersonal ketamine-induced experiences, and can verify the striking similarities between both phenomena (i.e., a sense of being dead, out-

of-body experience, feelings of levitation, transcendence of time-space continuum, life review, visits of non-physical realities, encounters with non-corporeal entities, ineffability of the experience, etc). It is important to note that the effect and phenomenology of NDEs in children (who have not yet developed any specific religious programming) are similar to NDEs in adults (Morse, Conner, & Tyler, 1985).

NDEs are often very transformative and can frequently induce positive changes in spiritual development and worldview (Ring, 1980, 1984; Ring & Valeriano, 1998). There are also numerous anecdotal accounts of patients who had a spontaneous remission of their illnesses (some of them were even classified as "terminal") after their NDE (Grey, 1985; Morse & Perry, 1992; Fenwick & Fenwick, 1995; Ring & Valeriano, 1998; Roud, 1990). Ketamine-induced NDEs appear to be equivalent to natural NDEs and may facilitate stable recovery by accelerating patients' psychospiritual growth and broadening their worldviews (Krupitsky & Grinenko, 1997).

#### **History of Ketamine in Psychotherapy**

A number of international psychiatric investigators have utilized treatment with ketamine to create cathartic effects in psychotherapy. In Iran, ketamine psychotherapy was shown very effective in treating various psychiatric disorders (Khorramzadeh & Lofty, 1973). These investigators administered ketamine to 100 psychiatric patients with different mental health and psychosomatic diagnoses, including depression, anxiety, phobias, obsessive-compulsive neurosis, conversion reaction, hypochondriasis, hysteria, tension headaches, and ulcerative colitis. They reported that 91 participants were doing well after six months, and 88 remained well after one year. These investigators concluded that "ketamine's abreactive or cathartic effect was related to its mind-expanding qualities;" however, they did not further specify their findings in clinical language. In Argentina, Fontana (1974) used ketamine as an adjunct to antidepressive psychotherapy in order to facilitate regression to a prenatal level through a disintegration and death experience, which was followed with a progression experience that was seen as similar to a rebirth. He emphasized the advantages of ketamine, which made it possible to achieve deep levels of regression. In Mexico, Roquet (1974) was the first clinician to employ ketamine psychedelic psychotherapy

in a group setting. He combined psychoanalytical techniques with the healing practices of Mexican Indian ceremonies and created a new approach to psychedelic psychotherapy that he called “psychosynthesis” (not to be confused with the same term used by Assagioli). He mainly used this procedure to treat neurotic patients, although he described some success with personality disorders and selected psychotic patients.

One of us (Krupitsky) first began using ketamine in the former Soviet Union in 1985 for treatment of alcoholism. He developed Ketamine Psychedelic Therapy (KPT) and treated more than 1,000 patients without complications. In one of his many controlled studies, nearly 70 per cent of his ketamine-treated patients remained abstinent from alcohol during a one-year follow-up, in contrast to only 24 per cent abstinence achieved in a control group treated with a more traditional form of therapy (Krupitsky, Grinenko, Berkaliyev, Paley, Petrov, Moshkov et al., 1992). In a comprehensive clinical research review on this subject, Krupitsky (Krupitsky & Grinenko, 1997) concluded that KPT is a safe and effective treatment for alcoholism and other drug dependencies, such as heroin and ephedrine, as well as effective for treatment of post-traumatic stress disorder, reactive depression, neurotic disorders, and avoidant personality disorders, and somewhat effective for the treatment of phobic neurosis, obsessive-compulsive neurosis, and histrionic personality disorder.

Krupitsky and his colleagues (Krupitsky, Burakov, Romanova, Dunaevsky, Strassman, & Grinenko, 2002) recently conducted a double-blind randomized clinical trial comparing the relative effectiveness of high (2.0 mg/kg IM) to low (0.2 mg/kg IM) dose administrations of ketamine for the psychotherapeutic treatment of heroin addiction; two-year follow-up data indicated that high dose ketamine was more effective. The study reported that “high dose KPT produced a significantly greater rate of abstinence in heroin addicts within the first 24 months of follow-up than did low dose KPT” (p. 277). The authors also concluded that “high dose KPT brought about a greater and longer-lasting reduction in craving for heroin, as well as greater positive change in nonverbal unconscious emotional attitudes” (p. 278). It appears the study’s data represent both a lower rate of recidivism and a higher degree of psychological integration. Recent changes in the regulations governing such research in Russia have now brought Krupitsky’s pioneering research efforts to a halt.

There was also an intriguing study at the University of Cambridge in the UK, in which ketamine was used to treat compulsive behavior in young women with anorexia nervosa with good results, although the publication of this study does not clearly indicate that the clinicians used a psychotherapeutic model (Mills, Park, Manara, & Merriman, 1998.) The study used infusions of ketamine to treat 15 patients with a long history of eating disorder, all of whom were chronic and resistant to several other forms of treatment. Nine responders showed prolonged remission when treated with ketamine infusions. Clinical response was associated with a significant decrease in Compulsion score: before ketamine, mean +/- SE was 44.0 +/- 2.5; after ketamine, 27.0 +/- 3.5 (t test, p = 0.0016).

There have also been various lone practitioners in other countries, usually family doctors or psychiatrists, who have used ketamine to treat psychological/psychiatric problems (see Jansen, 2001.)

### **Ketamine-Enhanced Psychotherapy**

Inspired by Krupitsky, one of us (Kolp) engaged in the clinical treatment of alcoholic clients using what he called Ketamine-Enhanced Psychotherapy (KEP). His approach was explicitly meant to replicate Krupitsky’s pioneering work and to extend it into another cultural context, the US (note: Kolp is a bi-cultural Soviet-American psychiatrist, who was originally trained as a Soviet psychiatrist, immigrated to the United States in 1981 and was re-trained as an American psychiatrist). As with Krupitsky’s KPT technique, Kolp’s KEP treatment explicitly relied on the transpersonal effects of ketamine to facilitate psychotherapeutic change. Both researchers have recently published their combined observations on clinical and empirical research of the effectiveness of ketamine-enhanced psychotherapy for treatment of alcoholism (Krupitsky & Kolp, 2007).

Once more, although most psychedelic drugs are illegal to use in the US even by physicians, ketamine is a notable exception because it is readily available to physicians as an anesthetic that can be legally used off-label for psychiatric treatment. Consequently, Kolp employed ketamine in his private psychiatric practice in the US from the fall of 1996 through the spring of 1999, administering it to more than 70 clients. Several of us also recently published Kolp’s empirical observations of the effectiveness of his KEP for treatment of alcoholism (Kolp, Friedman, Young, & Krupitsky, 2006).



During this same period of time, Kolp had an opportunity to administer KEP to two patients with end-stage cancer. This paper summarizes these patients' responses and provides Kolp's informal retrospective observations on ketamine's effectiveness for treatment of existential anxieties in terminally ill people. We emphasize that these clinical administrations were not conducted in a formal research context and this paper provides the informal retrospective observations on ketamine's effectiveness for treatment of existential anxieties in terminally ill people. However, in light of the recent resurgence of psychedelic research in the US and our plans, as a research team, to now seek institutional review board approval and grant funding for formally pursuing studies on ketamine's effectiveness in a number of clinical applications including the treatment of death anxiety, a reporting of Kolp's clinical observations is seen as warranted.

### **Method and Results**

KEP was offered to hospice clients for AGR in order for terminally ill patients to experience a "death rehearsal." KEP was administered to clients as part of a time-limited individual outpatient treatment that consisted of five sessions administered in the following stages:

#### **Session 1**

Assessment for appropriateness of treatment with KEP

#### **Session 2**

Establishment of a therapeutic alliance and formation of a psychotherapeutic "myth"

#### **Session 3**

Preparation for the transpersonal experience and formulation of the psychospiritual goal for the ketamine session

#### **Session 4**

Induction of the transpersonal experience through the administration of 150 mg of ketamine intramuscularly

#### **Session 5**

Integration of the transpersonal experience

The course of treatment was structured on a weekly basis with one session per week. Sessions 1-

3 and 5 were 75 to 80 minutes long and session 4 (ketamine-induced near-death experience) was 3 hours long. During the first three sessions the patient's beliefs about "afterlife" and attitudes toward the death were explored. The patient was told that the psychedelic session may induce important insights concerning the above beliefs and attitudes. An individually tailored "psychotherapeutic myth" was formed during this stage. During the fourth session the patient was injected with ketamine and instructed to surrender fully to the experience. The patient was then exposed to specially chosen music (generally, New Age composers). During the final session the patient, with the aid of the therapist, discussed and interpreted the personal significance of the symbolic content of the transpersonal experience. This uniquely profound and powerful transpersonal experience may help the patient to generate new insights and attitudes about the death and dying.

### **Results from Two Case Studies**

In order to illustrate how KEP affected clients with end-of-life existential issues, two representative case studies are presented. The first case demonstrates a success story, while the second case represents a failure to resolve anticipated grief. These two case studies are informative for understanding how KEP might be effective for treatment of anticipated grief resolution, and they also shed light on factors that can diminish the therapeutic benefits of KEP.

#### *Case Study 1*

W developed advanced (stage IV) breast cancer when she was 62 years old. By the time she was referred to an oncologist the cancer had already spread to the bone. She was diagnosed with osteolytic metastases (the cancer began eating away the bones of her spine, legs, and pelvis), which caused her persistent skeletal pain. The oncologist offered her an experimental chemotherapy, which W initially accepted. However, W learned that the prognosis of metastatic breast cancer is very poor and that the treatment with an investigational agent does not prolong survival time, which is limited to a few months after diagnosis. In addition, she immediately developed severe side effects (fatigue, loss of appetite, nausea, vomiting, worsening of bone pain) and stopped the treatment after the third intravenous administration. She was referred to a hospice program for palliative care and started treatment with an analgesic (morphine, 20

mg. orally, every 4 hours), an anti-anxiety medication (Lorazepam, 2 mg. orally, every 6 hours), and an anti-emetic agent (Metoclopramide, 10 mg. orally, 30 minutes before meals and bedtime). It was at this point that she requested ketamine-enhanced psychotherapy (KEP) in order to experience “death rehearsal.”

W shared that she was raised as the only child in an affluent family and did not have any significant childhood traumas. Her mother was Roman Catholic and her father was Unitarian Universalist. W initially adopted her mother’s religious beliefs, she later changed to her father’s views (between ages 8 and 9), and in her early 20s she adopted agnosticism as her primary life philosophy.

Her substance use history was unremarkable. W never smoked tobacco and never used any “hard” drugs. She did not start using alcohol until the age of 21, when she started drinking ETOH very infrequently, consuming a glass of a table wine, 1-2 times a year. W reported that she never tried any psychedelic drugs, including cannabis.

W identified herself as a “sex and love addict.” She shared that she was sexually awakened at the age of 8 by her 10-year-old cousin, who taught her “the art of self-pleasuring.” They practiced mutual masturbation in a variety of forms, on a regular basis (frequently daily), and, 4 years later, her cousin engaged another participant in their sexual explorations, an older boy, who was 15 year old at that time. That liaison lasted for a year until her family moved out of the area. W began dating independently at the age of 15 and remained very sexually active through her entire life. She never considered her sexual behavior to be aberrant or immoral, and she always unreservedly enjoyed her sexuality.

W reported that she devoted her life-long career to “a research of human sexuality.” She graduated from college with a social science degree at age 22 and started traveling extensively around the world, “sampling men of all races and colors.” She estimated that she had sex with more than 5,000 males and approximately 100 females.

She unintentionally became pregnant at age 39, giving birth to a healthy daughter whom she raised as a single mother. After her daughter started an exclusive boarding school, W decided to continue her own education as well and completed a doctorate in psychology. She became specialized in couples counseling and continued practicing her specialty until the time of her terminal illness.

Once W learned her prognosis, she became very frightened of her impending death. She also became preoccupied with her childhood religious indoctrinations and started having uncontrollable fears of “going to the Hell” as a punishment for her “morbid sin of lust.” She tried returning to her Catholic roots and even participated in confession; however, this provided no relief of her death anxiety. W remained very fearful and apprehensive, to the point she developed frequent “attacks of terror” several times a day, lasting from several minutes to half an hour. W continued having daily panic attacks despite ongoing treatment with an anti-anxiety agent.

W started treatment with KEP within one week after she terminated her chemotherapy. She spent three 75 to 80 minutes sessions sharing her life history, spiritual views, and beliefs about afterlife. During the preparatory stage of her psychotherapy, W was offered the option of either decreasing or discontinuing the doses of both CNS depressants (Lorazepam and morphine), in order to decrease the chance of amnesia and increase the chance of a mystical experience during KEP. W agreed with this plan and was successfully detoxified from Lorazepam by decreasing the dose by 1 mg every 24 hours. She was also able to gradually decrease the dose of Morphine from 20 mg. 6 times a day to 10 mg. 4 times a day. Moreover, she completely stopped taking opiates 8 hours prior to the KEP session. The half-life of morphine is approximately 2 hours; therefore, 8 hours of abstinence from the drug should have been sufficient time for the opiate to clear from the patient’s system.

W received 150 mg of ketamine intramuscularly during her fourth session. This dose induced “a near-death experience,” which lasted for 50 minutes. She described the following ketamine-induced transpersonal experience:

*My mind hastily left my body and I found myself in the heart of nothingness. There was no space, no time, no movement, nothing at all. I knew I was dead and felt disappointed that I did not have a life review. As soon as I thought about the life review though, I started rapidly re-living my entire life. I saw my birth, re-experienced my early childhood and adolescence, witnessed my young adulthood, and re-lived again my motherhood.*

*I also re-experienced all my sexual encounters and love affairs, viewing them not only from my personal perspective, but also from the point of view of my partners. I was gratified to know that my sexual behavior did not hurt my lovers at all. Quite to the contrary, I*

*learned that my lovemaking was the source of an intense pleasure for every one of my paramours and that my gift of sexual magic enriched their lives.*

*I then suddenly transcended into my previous lives and was shown that, from the beginning of Creation, I was made to be an amorous priestess of love, whose destiny was to enlighten people through sexuality. I did not feel that I was being judged whatsoever, and my shame and guilt were gone instantly. At that very moment I was swiftly transported into the brilliant light and felt the presence of my Creator. I sensed—with a great relief—that Creator is not a god of my mother, punishing and wrathful, but a benevolent god of my father - a unified force of Nature. I became clearly aware that death does not exist and recognized—without any doubts—I will be re-born again....*

The following week, during her fifth session, W happily shared that her persistent pain and recurrent panic attacks were completely gone and she was able to discontinue taking both morphine and Lorazepam. She remained comfortable until her death seven months later and did not require treatment with either pain-killers or psychotropic medications. Her daughter later reported that during the time of her death W was peaceful and content, and that she died with dignity and smile on her face.

### *Case Study 2*

L was a 46-year-old male who had developed a second attack of cancer. He had his first encounter with cancer at age 39, when he was diagnosed with bone cancer (chondrosarcoma of the left lower extremity). L underwent surgical treatment (amputation of the left leg) with follow-up chemotherapy and remained symptom-free for almost 7 years.

L developed painless jaundice 2.5 months prior to his treatment with ketamine-enhanced psychotherapy (KEP), followed by a diagnosis of advanced pancreatic cancer that at time of diagnosis had already become metastatic. He learned that for this type of cancer the median survival from diagnosis is around 3 to 6 months, and that the survival improvement with the combination of all available treatments is on the order of less than four weeks. L refused the most common surgical treatment for pancreatic cancers involving the head of the pancreas and declined both chemotherapy and radiotherapy. He was accepted by a hospice and it was at that point

that L requested KEP in order to accept his “dying and impending death.”

L was raised by an interfaith couple. His father was a Buddhist who shared with L his beliefs in an “afterlife existence” and “reincarnation of soul.” His mother was an atheist who did not believe in the existence of soul and afterlife; she taught L that “we came from the void and we are to go into the void.” His parents divorced (due to his mother’s infidelity) when L was 12 years old. He initially lived with the “party hardy dad” for 2 years and then moved to live with the “disciplinarian mom” for the next 4 years. He began living independently at age 18 and was self-sufficient from that point on.

At the age of 21, L married an older 34-year-old woman after the couple had dated for two years. They had one son, who was 24-years-old at the time of his father’s terminal illness. Father and son had a very distant relationship, and L did not talk with his son for more than five years. L and his wife divorced six years after the consummation of the marriage due to his extramarital affairs. After the divorce was finalized, his wife was awarded primary custody of the child and L became a visitation parent. Once the couple divorced, they stopped communicating with each other.

L was a “hermit” and lived in the “deep country” in his own rustic dwelling with a breathtaking view of a lake and tropical jungles. He had lived alone since age 26 and supported himself by growing and selling cannabis. Although he had been dealing illegal substances for many years, he never had any trouble with law or authorities.

L started using alcohol at age 15 and began smoking tobacco at 16. Alcohol was never his “cup of tea,” as he used it only a few times a year and eventually stopped drinking after age 26. L also stopped smoking tobacco when he turned 29 (he used to smoke 4-5 cigarettes, 3-5 times a week). His drug of choice became cannabis, which he started using at age 15 and continued to use daily, both smoking and eating, throughout the remainder of his life. L was consuming anywhere from 1 to 2 ounces of cannabis per week. He also “experimented” with psychedelic drugs and liked them very much, having “tripped” on LSD more than 200 times, “magic mushrooms” more than 500 times, and “peyote” more than 50 times. On several occasions, he also tried DMT, PCP, and MDMA.

At the time of his KEP, L was taking morphine, 20 mg, 6 times a day, and Xanax, 2 mg, 6 times a day. He

was also smoking cannabis, 10-12 “joints” a day, and in addition, was eating 3-4 “brownies” a day (he increased the consumption of cannabis to more than 2 ounces per week and moreover started consuming potent hydroponically-grown “super weed”). L was offered the option to stop cannabis and decrease the doses of both CNS Depressants (opiates and Benzodiazepine) in order to increase the chance of a positive transcendental experience during KEP; however, L opted to continue taking the above combination of psychotropic substances.

L had three preparatory sessions in the comfort of his own home on a one-to-one basis, each session lasting from 75 to 80 minutes. L then undertook KEP, with the session lasting about 3 hours. L described his ketamine-induced experience as follows:

*As soon as drug started working, my mind separated from my body and, in turn, started going into oblivion. I realized I am dying and a strong fear of non-existence completely overwhelmed me. My mind was finally gone and I was sucked into an infinite ocean of unconditional sorrow. Some part of me—the one of an observer—continued existing; however, it began decaying as well. I died as a human many times, each time from different causes, somehow re-incarnating again, each time regressing on a lower level. I then started dying and re-incarnating as a mammal, again regressing from higher forms to lower ones, next as a bird, after that as a fish, and so on, until I became a primordial protoplasm, at which point I blacked out. Only when the drug stopped working did I recognize that I was still alive. It was the worst bummer (a bad “trip”) I’ve ever had...*

During the last follow-up session L continued verbalizing his horror of disintegration all through his frightening experience of stepwise regression from existence to non-existence. Although he used the word “re-incarnation” (most likely a residue of his father’s religious beliefs), L utilized this word to describe a slow and painful death, not a proof of life after death. He also repeatedly stated that he “now knows for sure his mom was right when she taught there is no life after death.” L was offered additional follow-up sessions; however, he declined any further treatment. L continued using his drug cocktail in escalating doses and died less than 2 weeks after our last session—alone, disheveled, and soiled—probably from the accidental overdose of the CNS depressants.

## Conclusion

Due to ketamine’s availability for off-label medical use in the US, its short duration of action that fits well into the current delivery system, and its long history of successful clinical applications in treating a variety of mental health problems outside of the US, it presents itself as an ideal psychedelic to research the effectiveness of psychedelic psychotherapy in the US. In addition to biochemical mechanisms that might explain its possible efficacy for treating a wide range of psychological/psychiatric problems, its presumed ability to reliably replicate experiences that are to a large extent similar to NDEs provides a plausible transpersonal mechanism for its possible efficacy. Due to its relationship to NDEs, ketamine may be particularly helpful for treating death anxiety in those with terminal illnesses, namely by providing an opportunity for a direct experience of personal existence as a non-physical being that aids decision-making and powerful experiential shifts in attitudes toward death and dying. In addition, NDEs are well known to induce dramatic psychological transformations in people, so ketamine-induced NDEs may also have the potential to successfully help dying people overcome their existential anxieties as well as to treat various psychological problems, addictive illnesses, and psychiatric disorders. It should be pointed out, however, that we believe a ketamine-induced psychedelic experience has no beneficial effect in and of itself. In fact, when ketamine is used in uncontrolled settings recreationally, it can lead to significant medical problems (Ricuarte, 2005). We firmly believe that the therapeutic relationship, as well as set (i.e., patient’s expectations toward the experience) and setting (i.e., context surrounding the experience), are paramount to the effectiveness of ketamine-enhanced psychotherapy (KEP). In order for the KEP sessions to cause positive transformative experiences, it is extremely important to carefully prepare patients for the KEP session, to attentively supervise them during the session, and to provide psychotherapy after the session to facilitate the integration of the ketamine-induced transpersonal experience and to help patients personally accept insights gained during the KEP session. Previous work by Krupitsky and Grinenko (1997) demonstrated the added value of ketamine above and beyond set and setting; the control group of the patients with the same set and setting who were injected with a placebo did not gain the same benefits as compared to the group of patients



receiving ketamine. For these reasons KEP is a specific psychotherapeutic technique structured to incorporate the therapeutic relationship, set, and setting to achieve maximal benefits.

In a previous paper some of us reported that clients who failed to respond well to ketamine treatment of alcoholism seemed to have a history of severe control issues and/or persistent difficulties in maintaining long-term interpersonal relationships (Kolp et al., 2006). From the first case study presented in this paper, we at least partially attribute the woman's positive treatment outcome to the fact that she never tried any psychedelics previously (a novelty factor) and had positive expectations or set toward it. She was also willing to stop benzodiazepine while decreasing her use of opiates, which made the experience stronger. On the other hand, from the second case study we hypothesize that the man's negative treatment outcome was due at least in part to his extensive history of psychedelic use (i.e., it was just "another bad trip" for him) and his unwillingness to stop, or at least decrease, his sedative medications (benzodiazepine and opioids) before the ketamine session. It is noted that both of these CNS depressants diminish an individual's response to ketamine and can cause amnesia of the event. They may also negatively affect ketamine-induced transpersonal experiences due to over-sedation. Therefore, we recommend reducing or eliminating use of these substances by patients prior to any future therapeutic clinical applications of ketamine. Perhaps they should now even be considered as a possible contra-indication for ketamine-enhanced psychotherapy. In addition to set and setting, we also learned from these two patients, as well as from some of our prior research with alcohol abusers, that the novelty of the psychedelic experience may be salient for successful problem resolution. Psychedelics are indeed 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"). For those with extensive histories of psychedelic use, however, there is a diminished chance that a ketamine experience will be all that unique and transformative, whereas for the novice psychedelic user, given proper set and setting, the experience can be profound.

Consequently we conclude that KEP used adjunctively within a carefully crafted set and setting does appear to be a promising technique for successful

resolution of anticipated grief for patients in the US. Of course, with informally gathered case studies and no use of control groups or blinds (i.e., placebos), nothing definitive can be concluded about the generalized effectiveness of KEP from these observations. In addition, any possible conclusions are further compromised because these data were presented and analyzed in a retrospective manner without the benefit of written records to substantiate them. Nevertheless, based on the solid research on ketamine's usefulness in psychotherapy conducted by several international research studies, it is interesting to speculate that KEP may be successfully used in this way within the US for AGR. Additionally, the case studies strongly suggest that a transpersonal explanation for KEP's possible efficacy may be warranted along with biochemical explanations.

In order to explore the possible usefulness of KEP in the US more fully, beyond what appears to be some initial clinical success (and suggested limitations) made by Kolp in his practice, we note it is crucial to replicate these results in larger, well-controlled studies. We have designed the protocol of a prospective single-site, double-blind, placebo-controlled, randomized, parallel group clinical trial of the efficacy of KEP for treatment of existential anxieties in hospice patients with end-stage cancer. Following patient selection and consent procedures, it is planned that clients will receive one session with ketamine or placebo on the fourth sessions of standard outpatient treatment with outcomes measured at baseline before KEP and then one, three and six months following discharge. One unique aspect of our planned study is that we explicitly hypothesize that transpersonal factors, such as changes in level of self-expansiveness (Friedman, 1983) and spirituality (MacDonald, 2000), are among the essential mechanisms in KEP's possible efficacy and we intend to carefully measure transpersonal variables in a standardized fashion, along with other important factors.

Another potential area of future research is to explore the similarities between ketamine-induced NDEs and NDEs triggered by natural causes, such as from injuries, strokes, heart attacks, epileptic seizures, low oxygen levels, low blood-sugar levels, and other similar factors. Perhaps one useful strategy for future study would involve the administration of a psychedelic dose of ketamine to persons who have previously had a "natural" NDE. Psychological measures collected before the administration of ketamine in order to determine some



baseline information about the past NDE, along with the same measures collected after the ketamine-induced NDE, could be used to compare both experiences.

The fact that ketamine is an FDA approved pharmaceutical and can now be legally prescribed off-label does circumvent many of the prejudicial concerns against conducting research that affects most other psychedelics in the US. Ketamine's lawful availability avoids the complex bureaucratic morass that must be navigated in researching other psychedelic substances, a process in which simply obtaining stringently restricted drugs for research purposes can take years to negotiate. In addition, the recent lifting of the ban on formal research on psychedelics in the US, which has opened the way for a number of important psychedelic studies that are now being conducted at major US universities (Friedman, 2006), leads to an exciting opportunity for expanding the already impressive line of therapeutic studies utilizing ketamine for treatment of addictive and mental disorders. Further, the recent study conducted by investigators at the National Institute of Mental Health (Zarate et al., 2006) reporting ketamine's positive effects among treatment-refractory patients with major depressive disorder adds to the legitimacy of examining ketamine's psychotherapeutic potential. The possible importance of psychedelics may lie in their ability to foster transpersonal experiences and not just on their neurobiological effects (Friedman, 2006). If transpersonal experiences can be further demonstrated both to be reliably produced through psychedelics, including ketamine, and to have salutary effects, this could dramatically change the way that many psychological and psychiatric conditions are treated. This could have broader social implications, such as a diminishment of the fervor, stemming in part from the fear of powerful transpersonal experiences, that at least partially contributes to the war on drugs now vigorously pursued within many contemporary Western societies.

In regard to using ketamine to treat death anxiety, given the current mandate for outcome-based treatments that are time-limited as dictated by third-party payers, further research into exploring the potential of ketamine is very important. In addition, in this era of non-clinical constraints based upon financial interests, the possibility of developing an effective treatment approach that is cost-effective, limited to a few sessions, and that facilitates the reduction of costly restrictive drugs while simultaneously alleviating pain and increasing peace, has tremendous

appeal. Whether the intrinsic value of psychedelic therapies is viewed from the financial aspect or from the more humane aspect, we believe there is tremendous value in pursuing further research that may alleviate the pain of those suffering with the final emotional hurdles of surrendering both peacefully and mindfully to the inevitable.

### Endnotes

1. "The appropriateness or the legality of prescribing approved drug for uses not included in their official labeling is sometimes a cause of concerns and confusions among practitioners. Under the Federal Food, Drug, and Cosmetics (FD&C) Act, a drug approved for marketing may be labeled, promoted and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred as "approved uses." This means that adequate and well-control clinical trials have been reviewed and approved by FDA. The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature. The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the appropriate labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling. With respect to its role in medical practices, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects that data on safety and effectiveness on which drug approval is based." (FDA Notice, 1994, n.p.)

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