KETAMINE FOR DEPRESSION: WHAT PSYCHOLOGISTS NEED TO KNOW

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ABSTRACT

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The emphasis of this study was on the role of the psychologist in patient care and/or as a member of a research team with respect to ketamine as a novel treatment for depressed, bipolar, and suicidal patients. Ketamine is synthetic medication that was discovered in the 1960s. It is classified as a dissociative anesthetic and is primarily used in anesthetic medicine. It is believed that ketamine works by disrupting the transmission of glutamate, an excitatory neurotransmitter. Specifically, ketamine acts as an antagonist of the NMDA receptor in the CNS. In recent years, ketamine has been shown to have a robust and rapid-acting but temporary antidepressant effect that begins to work within hours of administration. The antidepressant effect of ketamine varies in its duration but clinical studies have shown that it often lasts for 1 to 2 weeks, and its effect can be extended by multiple administrations. However, ketamine is a controversial treatment because it induces a temporary dissociative or altered state in recipients. This aspect of ketamine treatment does not bother most patients, especially if they are prepared for it. However, the medical community has traditionally been strongly biased using agents that create psychedelic experiences. This study reviewed the existing literature on using ketamine to treat patients with severe and refractory depression, bipolar disorder, and suicidal ideation as well as other aspects of what is currently known about ketamine. Specific roles and responsibilities of the clinical psychologist regarding therapeutic ketamine

treatment were discussed. Gaps in the current literature on ketamine were explored at length and suggestions for several new directions for research were made.

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CHAPTER I: INTRODUCTION

Ketamine is a synthetic chemical that has been used in anesthetic medicine for over 50 years. It is a highly hallucinogenic material that can induce a psychedelic, dissociative and/or transcendent experience in users. Recently, ketamine was discovered to have profound antidepressant properties as well. Ketamine's antidepressant effect was first noted by Berman in 2000 and has been further established by Zarate et al. (2006), Zarate et al. (2012), Murrough et al. (2012), and others in controlled clinical experiments. Ketamine appears to work by affecting the glutamate pathway in the central nervous system (CNS). It is of great interest to researchers and clinicians because of its potential as a rapid-acting antidepressant, taking effect within hours of administration.

Problem Statement

Although all psychologists receive training in basic psychopharmacology, hardly any seem to know about ketamine. Part of this may stem from the fact that virtually all of the research that has been done on the therapeutic uses of ketamine has been by psychiatrists and has been published in medical journals. Further, research on the therapeutic uses of ketamine is still in its infancy, there are significant problems with the existing research, and there are many more questions that need to be asked. It is essential for psychologists to be knowledgeable about ketamine both to provide the best possible outcomes for their patients and also to contribute to the growing research efforts and to push this field forward.

Purpose Statement

The objectives of this clinical research project were to further the understanding of the therapeutic uses of ketamine for the treatment of depression (and related disorders), to critically examine the existing research on this topic, and to discuss the role of psychologists in both research and patient care with respect to therapeutic ketamine treatment. These objectives were accomplished through a comprehensive, integrative literature review that brought together the essential information about ketamine in one place.

Significance Statement

Millions of people worldwide suffer from depression in its various forms and thousands of people die by suicide each year. It is possible that ketamine (or a yet-to-be discovered derivative) could reduce the suffering of some of these people and even save people's lives. Presently, there are no other fast-acting treatments for depression and there are no other treatments at all for acute suicidal ideation. For these reasons, the continued study of ketamine is imperative.

Definitions of Key Terms

- Anesthetic: An anesthetic agent is one that causes a temporary state of loss of consciousness, loss of memory, lack of pain, and relaxed muscles.
- Analgesic: An analgesic agent is synonymous with a painkiller. It provides temporary relief from pain.
- Bioavailability: The amount of the medicine that reaches the bloodstream.

- Dissociative: Dissociative agents are ones that produce temporary feelings of detachment from one's environment and/or one's sense of self. Many but not all dissociative agents are also hallucinogenic.
- Drug schedule: The drug scheduling system was created by the U.S. government in 1970 to regulate the manufacture, importation, possession, use, and distribution of certain medications and illegals drugs. Two federal agencies, the Drug Enforcement Administration (DEA) and the Food and Drug Administration (FDA), both contribute to determining which substances are placed into the five schedules or categories based on the substance's perceived medical usefulness and potential for abuse. Ketamine is currently categorized as Schedule III-N, signifying that it is legal for physicians to use this medicine, it is a controlled substance, and it is considered nonnarcotic.
- FDA approved: The FDA is the federal agency responsible for protecting public health through the regulation of pharmaceutical and food products among other things. Ketamine has been FDA approved for use in anesthetic and analgesic medicine since the 1970s; however, ketamine is not currently FDA approved as a treatment for depression so its use in this way is considered experimental. The antidepressant use of ketamine is scheduled for FDA review in 2017.
- Hallucinogenic: A hallucinogenic agent causes perceptual distortions (e.g., auditory, tactile or visual hallucinations). Hallucinogens can also cause alterations in a user's cognitive, spiritual and/or emotional sense of reality.
- Egolytic: Derived from the root words meaning breaking of the self, it refers to the time, usually under the influence of mind-expanding drugs, when one realizes

how small one is in relation to the cosmos and lets go of ego-oriented or self-involved needs and opens up to a greater sense of unity or purpose.

- Emergence reaction: An emergence reaction occurs when a patient has been given ketamine (or a medication similar to it) as a surgical anesthetic, and upon emerging from the anesthesia the patient reports feeling disoriented, confused, agitated, or seeing bizarre imagery. Most often, emergence reactions occur when the patient has not been adequately prepared for the psychoactive component of the anesthetic medicine. Appropriate treatment for an emergence reaction is supportive verbal care and/or the use of additional medications, if needed.
- Glutamate: Glutamate is an excitatory neurotransmitter found throughout the CNS of vertebrates, including humans. It is thought to play an important role in basic psychobiology of learning and memory. Ketamine temporarily interferes with one part of the glutamate signaling pathway.
- NMDA: This is the abbreviation for the N-Methyl-D-aspartate receptor. This is one of many kinds of glutamate receptors in the CNS, and it is the specific one that ketamine binds to and temporary disables, disrupting the transmission of the glutamate signal.
- Psychedelic: Psychedelic comes from root words meaning "mind manifesting." A psychedelic experience refers to a nonordinary state of consciousness, often reached through the use of psychoactive drugs but also specific spiritual practices, in which aspects of one's mind or the nature of reality that were previously inaccessible become accessible. Psychedelic experiences may or may not include hallucinations and may include extreme sensitivity to one's environment, or

conversely, a disconnection from one's environment and a heightened sensitivity to one's internal world.

- Psychotic experience: Psychotic experience generally refers to a distortion of or disconnection from reality resulting from mental illness. Psychotic episodes are frequently described as frightening and/or chaotic.
- Psychotomimetic: Psychotomimetic agents temporarily induce some symptoms of psychosis such as mimicking psychosis. These agents are primarily used for studying mental illnesses such as schizophrenia. At one time, lysergic acid diethylamide (LSD) was used as a psychotomimetic agent. Ketamine was also briefly used as a psychotomimetic agent in the 1990s. The term "psychotomimetic" is sometimes used pejoratively to refer to a psychedelic experience.

CHAPTER II: LITERATURE REVIEW

Ketamine is a synthetic chemical that has been used for over five decades as a highly safe anesthetic agent (Naughton, Clarke, O'Leary, Cryan, & Dinan, 2013). It is currently used in both humans and animals as a dissociative anesthetic that is fast acting and well tolerated. Ketamine is also known in the public realm for its recreational use as it produces euphoric and psychedelic effects. Its primary mechanism of action is thought to be as an antagonist of the NMDA receptors in the CNS, which are important in the signaling pathway of glutamate, an excitatory neurotransmitter.

Clinical research since 2000 supports an additional promising use for ketamine as it has been found that low to moderate doses of the medicine produce extremely rapid antidepressant effects in patients with certain mood-related disorders including major depressive disorder (MDD), bipolar disorder, and suicidal ideation (Naughton et al., 2013). The present study investigated the antidepressant properties of ketamine for use with adult patients with severe depression, refractory or treatment-resistant depression, bipolar disorder, and/or suicidal ideation and examined ketamine's potential as a new therapeutic treatment for these populations.

A broad background on ketamine, including its history, chemical makeup, and mechanisms of action is provided, and its previously established uses both as an anesthetic agent and a street drug are profiled. This is followed by an in-depth literature review of current research on ketamine's therapeutic uses, detailing the available routes of administration and the notable populations in which therapeutic ketamine has been researched, including patients with MDD, bipolar disorder, and suicidality. Then, given

that ketamine induces a dissociative and/or psychedelic effect in patients, a very brief introduction to psychedelic medicines is offered as a context for thinking about the therapeutic uses of substances that cause a temporary alteration in consciousness or perception. Specifically, the works of Leary and Grof are summarized.

Ketamine's Discovery

In 1962, Calvin Stevens, a scientist working at Parke-Davis, created CL-369, which was renamed CI-581 (for its clinical investigation) and finally termed ketamine (Jansen, 2004; Kumar, n.d.). Ketamine was first developed as a derivative of and hopeful replacement for phencyclidine (PCP, also known as angel dust), another highly hallucinogenic but medically effective dissociative anesthetic that was known for producing scary, nightmarish visions (Jansen, 2004). In 1964, ketamine was administered to humans for the first time, and by 1966 Parke-Davis patented the drug as an anesthetic to be used in humans and animals (Jansen, 2004). Interestingly, ketamine (or anything similar to it) is not found anywhere in nature; it is a completely synthetic drug that has never been observed naturally in animals or plants. This differs considerably from most other drugs that produce psychedelic effects as they typically have plant analogues. Ketamine has none (Jansen, 2004).

Ketamine was granted FDA approval in 1970, and it was first used medically as an anesthetic administered to American soldiers in the field during the Vietnam War (Kumar, n.d.). Vietnam War veterans are also thought to be the first recreational users of ketamine. Following the war, ketamine became a popular surgical anesthetic used around the world for adults, children, and the elderly despite its potential for producing emergence reactions (e.g., disorientation upon waking; Naughton et al., 2013).

While ketamine is primarily used in anesthetic medicine, it has also been of interest to psychiatrists and psychotherapists as tool for learning about mental disorders and/or as an adjunct to psychotherapy. The modern discovery of ketamine as a rapid-acting antidepressant can be traced back to the work of psychiatrist John Krystal and his team at Yale University who were attempting to learn more about psychosis in the 1990s. They administered ketamine to healthy volunteers and schizophrenic patients to deliberately induce dissociative states (Krystal, 1998, as cited in Sewell, 2007). Krystal reported that the antidepressant effect was huge and obvious in the schizophrenic patients, although incidental, and that some patients with schizophrenia specifically requested more ketamine treatments to alleviate their depressive symptoms. Although Krystal's research was suspended due to concerns from community watch groups about administering psychedelic drugs to "helpless" mental patients, investigations into his team's conduct and methodologies were found to be sound and ethical (Sewell, 2007). In any event, Krystal's findings caught the attention of the research community and paved the way for future research on ketamine's potential uses as an antidepressant.

Ketamine in Anesthesia

Much of what is known in general about ketamine comes from its use in anesthetic medicine. Since its FDA approval as an anesthetic agent for humans, ketamine has been administered to several million patients worldwide (Naughton et al., 2013). Its widespread usage is due to its well-established safety profile as well as its unique properties that set it apart from other anesthetic agents. Unlike other anesthetics that typically depress the circulatory and respiratory systems, ketamine slightly excites the circulatory system and does not lead to the depression of respiratory function (Krystal,

Sanacora, & Duman, 2013). It is often the anesthetic of choice when the patient has experienced a lot of trauma or blood loss, and it is frequently used in roadside emergencies and military field hospitals (Stevenson, 2005). Ketamine is also used in lower doses as "office anesthesia" because it is metabolized so quickly, allowing patients to safely drive themselves home after it wears off (Jansen, 2004).

The anesthetic state induced by ketamine is marked by superficial sleep and profound analgesia as brain pathways are only selectively interrupted, ultimately leading to somatesthetic (body awareness) sensory blockade accompanied by hemodynamic stability (related to the maintenance of blood pressure and blood flow), airway reflex preservation, and spontaneous ventilation (DailyMed.com, 2013; Stevenson, 2005). Therefore, patients appear to be in a cataleptic state in which voluntary movements are suppressed while involuntary and automatic actions such as heart function, respiration, and peristalsis (digestion) continue uninterrupted (Kumar, n.d.; Naughton et al., 2013).

The drug's excellent safety profile has led to a "massive revival of interest in ketamine by anesthetists, emergency doctors, and pain specialists" (Jansen, 2004, p. ix). Ketamine is regarded as a particularly safe anesthetic choice for fragile populations, especially in emergency settings, children, and elderly patients (Jensen, 2004; Turner, 1994) because of its lack of depression of cardiac function and its wide safety margins. Unintentional medical overdoses of ketamine have been recorded; however, in each case patients experienced a prolonged but complete eventual recovery (DailyMed.com, 2013). In cases of accidental medical overdose, the patients who eventually recovered received 10 times the dose normally used to produce a surgical anesthetic effect, and there is an

established wide margin between the highest used medical dosage and a lethal dose (DailyMed.com, 2013; Jansen, 2004).

To produce surgical anesthesia via intravenous (IV) administration, ketamine's dose parameters fall between 1 to 4.5 mg/kg of body weight with an average dose of 2 mg/kg as standard (Drugs.com, 2014). At this dose, onset occurs rapidly, typically within 30 sec with duration of 5 to 10 min after which the anesthetic effect may be prolonged with additional infusions. To produce surgical anesthesia via intramuscular (IM) administration, 9 to 13 mg/kg is typically used with a 3 to 4 min onset and duration of 12 to 25 min (DailyMed.com, 2013). For nonsurgical anesthesia, including short procedures where only a single anesthetic is used, the dose parameters are slightly lower, at 0.5 to 2 mg/kg for IV administration and 4 to 6 mg/kg for IM administration.

In addition, to produce analgesia effects subanesthetic doses of 0.15 to 0.25 mg/kg via IV administration are used to relieve pain (Kumar, n.d.). It should be noted that a dose of at least 1 to 2 mg/kg is thought to be necessary to produce intense dissociative or hallucinogenic effects though smaller doses do result in less severe feelings of an altered state or perceptions (Drugs.com, 2014).

Ketamine's Chemistry

As previously noted, ketamine is chemically related to phencyclidine (PCP or angel dust), although ketamine's effects are much shorter acting and produce much less distortion of reality (Jansen, 2004; Kumar, n.d.). Chemically, ketamine is classified as an arylcyclohexylamine. Its full chemical name is 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (U.S. Patent No. 3,254,124, 1966). Ketamine is a chiral compound, meaning that there are two symmetric versions of the ketamine molecule. Chiral

molecules are like human hands: they are virtually identical except that one cannot fit one's right hand into one's left glove. Likewise, ketamine has two versions or enantiomers, designated S(+) and R(-). This fact is important because the different enantiomers of ketamine may differ in their ability to bind to their target receptor sites, their effectiveness as antidepressants, and/or their psychedelic effects (Kumar, n.d.; Stevenson, 2005). Further research on these aspects of ketamine is currently underway.

Ketamine's Mechanism of Action

Ketamine's biochemical mechanism of action is not fully understood though research has started to unravel the mystery of how ketamine produces its anesthetic, analgesic, and antidepressant effects (Krystal et al., 2013). It is known that within certain parts of the cortex and thalamus, ketamine selectively depresses neuronal function while at the same time it stimulates parts of the limbic system, including the hippocampus (Kumar, n.d.). Within the midbrain and thalamic areas in particular, it has been established that ketamine produces functional disorganization of nonspecific pathways. In addition, ketamine interferes with pain transmission, specifically within dorsal horn neurons of the spinal cord (Kumar, n.d.).

Ketamine produces its effects through multiple actions. Most important, ketamine is an NMDA receptor antagonist that affects the glutamatergic system. In other words, ketamine belongs to a class of anesthetics that antagonize, or inhibit, the actions of NMDA receptors (Krystal et al., 2013; Naughton et al., 2013). NMDA receptors, found throughout the CNS, allow electrical signals to travel between neurons of the brain and of the spinal column. The neurotransmitters glutamate and glycine must bind to the NMDA receptor in order for it to be open and activated.

There are several types of NMDA antagonists, including competitive, uncompetitive, and noncompetitive types. Noncompetitive NMDA antagonists, such as ketamine, bind both directly to the open channel ion pore and to an allosteric (neighboring) site on the NMDA receptors, preventing excitatory neurotransmitters, such as glutamate, from activating these receptors (Krystal et al., 2013; Naughton et al., 2013). Other NMDA receptor antagonists include amantadine, chloroform, methoxetamine, and selfotel.

As previously noted, glutamate is an excitatory neurotransmitter responsible for triggering electric impulses and "turning on" cells (Jansen, 2004). Glutamate is found nearly exclusively intracellularly, or inside cells, and does not cross the blood-brain barrier (Purves et al., 2001). Glutamate is most heavily concentrated in nerve terminals. Virtually all excitatory neurons located within the CNS contain glutamate (Purves et al., 2001). Thus, glutamate is known as one of the most crucial transmitters for normal and healthy brain function including cognition, learning, and memory.

In order to understand ketamine's mechanism of action, it is also important to understand the role of glia, or support cells, in the nervous system. One of the roles of glial cells appears to be deactivating glutamate and/or regulating glutamate levels (Krystal et al., 2013). However, the current leading hypothesis is that people with depression have glial loss, possibly due to a variety of mechanisms or factors. (For a more detailed discussion of this topic, please refer to Krystal et al., 2013). This glial loss may cause a dysregulation in glutamate levels, which ultimately leads to the loss of dendritic spines and dendritic atrophy through a complex chain of reactions (Krystal et al., 2013). This correlates with the neuronal atrophy and synapse loss that is observed in

people and animals who are severely depressed (Krystal et al., 2013). Ketamine appears to work by blocking or disrupting the glutamate signal at an essential step in the chain, promoting the rapid regrowth of dendritic spines and the formation of new neural connections, which, in effect, creates the observable antidepressant effect that persists beyond the time that the drug is metabolized out of the patient's body (Duman & Li, 2012; Kavalali & Monteggia, 2012). (This is a simplified version of ketamine's mechanism of action; for a fuller discussion, please refer to Berman et al., 2000, Carlson et al., 2013, and/or Krystal et al., 2013.

Further evidence for this understanding of ketamine's mechanism of action comes from the following discoveries. In patients with depression, chronic stress and depressive symptoms appear to result in neurotrophic atrophy (Duman & Li, 2012). In limbic structures of the brain, such as the hippocampus and prefrontal cortex, long-term stress has been observed as leading to structural alterations marked by changes in dendrite length, spine density, and neurogenesis regulation (Duman & Li, 2012). Conversely, as a part of ketamine's mechanism of action in which it increases the synthesis of synaptic proteins and stimulates the mammalian target of the rapamycin signaling pathway, its administration results in the induction of synaptogenesis and increased spine formation in the prefrontal cortex (Duman & Li, 2012). Therefore, ketamine can reverse the atrophy of neurons found in the prefrontal cortex in an extremely rapid manner (Duman & Li, 2012).

Kavalali and Monteggia (2012) further explained that the blockage of NMDA receptors that ketamine causes also deactivates eukaryotic elongation factor 2 (eEF2) kinase, thus leading to the desupression of rapid dendritic protein translation (Kavalali &

Monteggia, 2012). Rapid dendritic protein translation may cause a decrease in brain derived neurotrophic factor (BDNF), a deficit that has been linked to MDD (Kerman, 2012). As a part of ketamine's effect on neural pathways, BDNF signaling is actually increased (Kerman, 2012). This mechanism, which affects synaptic plasticity, is what is thought to facilitate ketamine's relatively long-term effects (Kavalali & Monteggia, 2012; Li, 2012).

Additionally, ketamine also interacts to a lesser degree with some opioid receptors, such as mu, delta, and kappa, resulting in some analgesic effects. Other actions include inhibiting monoaminergic pain pathways, altering cholinergic neurotransmission, and inhibiting nitric oxide synthase, all of which are related to perception of pain and thus result in analgesia (Kumar, n.d.).

Metabolism of Ketamine

Ketamine is metabolized at a rapid rate, with a half-life of 180 min in humans (Naughton et al., 2013). This rapid metabolization means that the mild psychotomimetic and dissociative effects appear approximately 30 min postadministration and dissipate within 80 min postadministration (Zarate et al., 2006).

Because of ketamine's short half-life in comparison to its relatively long lasting antidepressant effects, it is now known that the underlying neurobiological mechanisms of ketamine's antidepressant effects are not as simple as the mere blocking of the NMDA receptors (Naughton et al., 2013). Rather, ketamine's mechanism of action includes a series of events in which the rapid antidepressant response observed is sustained for a duration of 1 to 7 days posttreatment, long after the ketamine has been metabolized and excreted (Naughton et al., 2013).

Effects of Ketamine

In addition to its anesthetic properties, as previously described, and its antidepressant effects that will be discussed in further detail shortly, ketamine also produces dissociative, euphoric, and/or psychedelic experiences in most users. According to one source, approximately 12% of patients receiving anesthetic ketamine experience an "emergence reaction" or unusual mental experience while transitioning back to full consciousness (DailyMed.com, 2013). These effects typically last no more than a few hours, and no residual or long-term negative psychological effects have been established as a result of them. While emergence reactions can be distressing, most patients describe them as pleasant, likening the sensation to being in a dream state with vivid imagery.

At lower doses, ketamine feels more like a stimulant; at higher doses, it acts more like a sedative (Jansen, 2004). While patients have reported experiencing psychedelic effects upon emergence after high anesthetic doses, psychedelic and dissociative effects are also felt at doses much lower than those used in surgical and clinical anesthetic settings (Turner, 1994). To produce a psychedelic effect, a dose that is only 10% to 25% of a typical anesthetic dose is necessary (Jansen, 2004). Dissociative and psychological side effects have also been recorded at low doses that are typically used for analgesic, therapeutic, and recreational usage.

However, lower doses appear to be more likely to induce a somewhat semialtered state rather than a full psychedelic experience marked by hallucinations or breaks with reality as could be observed in higher doses. Additionally, the intensity of these effects is related to both the amount of ketamine ingested and the route of administration. In

particular, this has been established by recreational users who appear to take different doses in order to achieve various effects. Though dependent on body weight, on average 10 to 20 mg induces a nonpsychedelic and dissociative altered state, 50 mg produces a semiconscious state without severe psychedelic experience, and 75 to 125 mg is a common dose taken to achieve a psychedelic experience, otherwise known as a ketamine trip (Turner, 1994). It is often at the 100 mg threshold that users report a break in continuity of consciousness in which a sensation of a lack of reality or stability is felt (Turner, 1994).

At a recreational dose, ketamine's effects are felt approximately 30 sec post-IV injection, 2 to 4 min post-IM injection, and 10 to 20 min postoral administration (Jansen, 2004). The route of administration also affects the duration of effects and how long it takes for normal function and cognition to return. IV administration produces the shortest duration of psychological effects at 10 min with IM administration producing a duration of 30 to 60 min, insufflation producing a duration of 1 hr, and oral doses lasting 1 to 4 hr (Jansen, 2004).

Thus, ketamine appears to have three major operational dose parameters, each tier producing different intended effects: recreational, therapeutic, and anesthetic. Table 1 summarizes the three tiers and their related dose parameters, available routes of administration, and notable effects.

Table 1

Operational Definitions for Ketamine Dosages

Tier	Level	Amount[a]	Amount for person weighing 150 lbs	Route(s) of administration	Notes
Recreational	Low	20 - 50 mg	n/a	Insufflated	May produce a brief "uplifting" effect but unable to produce a profound antidepressant effect.
	Medium	50 - 100 mg			
	High	> 100 mg			
Therapeutic	Micro	10 - 40 mg	n/a	Oral, nasal, or sublingual	Taken on a regular basis (daily or semiweekly), this regimen might help extend the effect of a ketamine treatment.
	Low	< 0.5 mg/kg	< 34 mg	IM or IV	
	Medium	0.5 - 1.0 mg/kg	34 - 68 mg		
	High	> 1.0 mg/kg	> 68 mg		
Anesthetic	Low	2 mg/kg	136 mg	IM or IV	
	Medium	4 - 6 mg/kg	272 - 408 mg		
	High	9 - 13 mg/kg	612 - 884 mg		

Note. [a]Some dosages are given in discrete amounts and some are given in relative amounts. All amounts produce an altered state to some degree. IM = intramuscular. IV = intravenous.

The psychedelic effects of ketamine are typically described as positive experiences of extreme spirituality or feelings of connectedness and love (Jansen, 2004). Ketamine may feel like being in touch with God, being engrossed in deep thinking, or

difficulty assessing what is real and what is illusion (Jansen, 2004). High doses of ketamine may also result in the sensation that one is in a different or alternate reality or that the external real world no longer exists outside the self. Ketamine users also sometimes have near-death experiences or the physical sensation of leaving one's body (Jansen, 2004). Near-death experiences typically only occur with the higher doses of recreational use (Jansen, 2004). Nonetheless, many recreational ketamine users, as well as medical patients who have experienced ketamine's dissociative or psychedelic side effects, report that theirs was a pleasant experience. Recovering forgotten memories, feelings of bonding and connectedness with others, insight into nature or existence, lucid dreaming, and creative problem solving are all positive experiences associated with ketamine's the psychological effects (Jansen, 2004).

When ketamine's dissociative or psychedelic "side effects" are perceived as undesirable, there are several strategies for mitigating them. Some patients experience fewer psychological side effects by simply lowering or dividing the dose (DailyMed.com, 2013). Additionally, administering benzodiazepines, especially diazepam, has been shown to be an effective strategy for decreasing the incidence of psychedelic experiences (Kumar, n.d.). In surgical settings where ketamine is used as an anesthetic, atropine and droperidol have been found to increase the frequency of emergence reactions while thiopentone has been shown to reduce incidences of emergence reactions. In addition, simply discussing potential psychological side effects and providing a quiet and peaceful environment for emergence also helps reduce discomfort (Kumar, n.d.).

Ketamine As a Street Drug and Its Abuse

When ketamine is used recreationally, it is referred to as "Special K" to distinguish it from its legal and medicinal uses. However, it is the same substance as ketamine is only produced pharmacologically. Because it is only created under controlled conditions and is exclusively available in a pharmaceutical vial, ketamine is considered to be much safer than other street drugs and virtually never contains impurities (Turner, 1994). Although ketamine was not produced until the 1960s, by the late 1970s the U.S. government was expressing concern about its abuse (Turner, 1994). Since the 1990s, recreational use has been marked by the youth subculture of techno and electronic music, particularly at raves and clubs (Jansen, 2004; National Institute on Drug Abuse [NIDA], 2010). Among younger teenagers (ages 13 to 18 years), prevalence of ketamine usage has varied between 0.8% and 2.5% since 1999 when tracking its usage first began (NIDA, 2010). Its use appears to have peaked around 2000, and in recent years its prevalence has been on the low end of the range (NIDA, 2010). Young adults ages 18 to 25 years are the most frequent ketamine users at a rate of 0.2% (National Survey on Drug Use and Health, 2006). An estimated 2.3 million people in the United States are thought to have tried ketamine recreationally at least once in their lifetime (National Survey on Drug Use and Health, 2006).

In recreational contexts, ketamine is typically insufflated (snorted) at a much lower dose than what is used for anesthetic effects (see Table 1; Turner, 1994). Powdered ketamine is made by taking pharmaceutical ketamine and dehydrating it by placing it in an oven and making it into a crystalline powder. The standard club "bump," or single insufflated dose, often averages around 50 mg. To achieve a psychedelic trip,

upwards of 100 to 200 mg is used (Jansen, 2004). Those who wish to achieve a psychedelic dose via IM administration typically take 50 to 100 mg. The average oral dose of recreational ketamine is 300 mg because ketamine is poorly absorbed in this manner (Jansen, 2004). It is worth noting that changing one's route of administration from snorting to injecting is often indicative of heavier use that comes with problematic use and/or psychological dependence (Jansen, 2004).

Although recreational users obtain and use ketamine illegally, some important information about the effects of ketamine has been obtained from studying this population, especially regarding the effects of long-term and frequent use that have not been studied clinically. Chronic ketamine abusers, or those who typically take large doses on a very frequent basis, show cortical white matter and gray matter deficits as well as altered cortical functional connectivity (Krystal et al., 2013). As a result, ketamine abusers have altered thought content and may show cognitive impairments (Krystal et al., 2013). Long-term ketamine abuse is also thought to be linked to biliary dilation (inflammation of the bile ducts) and cystitis (stiffening or irritation of the bladder; Krystal et al., 2013).

Deaths in which ketamine was the sole drug responsible are quite rare though they have occurred (Jansen 2004; Lalonde & Wallage, 2004). More typically, fatal overdoses related to the recreational ketamine use occur either when it is combined with another drug or other factors such as the user drowning or falling. Nonetheless, although there is little risk of death due to ketamine overdose there have been a small number of such deaths recorded (Turner, 1994). If very large doses in line with anesthetic amounts are

administered repeatedly, ketamine may induce unconsciousness, cardiovascular system failure, and eventually death (Jansen, 2004).

While it is speculated that ketamine is not physically addictive in the same manner that alcohol, cocaine, and heroin are, no large-scale studies have been done and there is conflicting terminology and thresholds for what is considered to be addiction (Morgan & Curran, 2011). Originally, it was speculated that ketamine is not physically addictive as it is not primarily dopaminergic nor does it primarily act on the opioid receptors although it does appear to have a very low affinity for some receptors in these pathways. However, some studies have demonstrated changes to the prefrontal cortex, possibly signifying that ketamine does lead to upregulation (increase) of dopaminergic receptors (Morgan & Curran, 2011). However, these same changes are observed after prolonged use of other drugs; thus, it cannot be stated with certainty that these changes occurred from ketamine use as opposed to their occurring from other drugs (Morgan & Curran, 2011).

Physical withdrawal symptoms from ketamine have also not been firmly established or observed (Jansen, 2004). It should be noted as well that PCP and other hallucinogens also do not have a code for withdrawal in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM–5*; American Psychiatric Association, 2013), which reads, "Significant withdrawal has *not* been documented in humans after repeated use of phencyclidine, other hallucinogens, and inhalants; therefore, this criterion is not included for these substances" (p. 484).

Though ketamine abusers may not be physically addicted to the substance, there is some evidence that ketamine may be psychologically addictive (Jansen, 2004; Morgan

& Curran, 2011; Turner, 1994). There are reports of individuals who have increased their ketamine doses to up to 600% over their original dosage and others who have continuously used ketamine until their supply was exhausted (Morgan & Curran, 2011; Turner, 1994). It has been noted that those with family histories of drug dependence, especially alcohol, are more likely to develop an addictive relationship to ketamine (Jansen, 2004).

In addition to ketamine's psychologically addictive properties, there is also evidence that it is possible to build up a tolerance to the drug with long-term use at fairly high doses (Jansen, 2004, p. 45). Studies with rats demonstrated that they will repeatedly self-inject with ketamine if it is freely available (Jansen, 2004). This type of long-term use after tolerance has been built shows similar effects in animals and humans; the same dose is more likely to produce stimulant-like effects rather than psychedelic effects, and an increase in dosage is needed to reach the ketamine high again (Jansen, 2004). This is because, like a stimulant, ketamine produces a new cyclical pattern in the user's dopamine pleasure system. The altered pleasure system then requires more dopamine to be stimulated, leading to higher doses and more frequent use (Jansen, 2004, p. 198). Tolerance to ketamine is marked, as a break of even several years may not reverse it in a long-term abuser (Jansen, 2004).

Side Effects and Risks of Ketamine Use

Although ketamine's excellent safety profile has been well established, there are certain risks and known side effects as with any drug. It is known from anesthesia patients that heart rate and blood pressure are frequently raised after ketamine administration (DailyMed.com, 2013; Stevenson, 2005). Though ketamine causes direct

depression of the myocardium (heart muscle), hemodynamic stability is still generally maintained because of ketamine's ability to stimulate the CNS (Stevenson, 2005). In normal dosage parameters, respiration is slightly stimulated and the airway reflexes are preserved (DailyMed.com, 2013; Stevenson, 2005). However, rapid IV administration of high doses of ketamine may lead to apnea or respiratory complications. Simultaneous administration with other respiratory depressants such as opioids may increase this risk. Additionally, despite respiratory system stimulation there is still an elevated risk of aspiration as ketamine leads to an increase in salivary and tracheobronchial secretions (Stevenson, 2005). Adverse reactions related to the eyes have also been noted: Ketamine at anesthetic doses may result in slightly elevated intraocular pressure as well as diplopia (double vision) and nystagmus (involuntary eye movements; DailyMed.com, 2013). Moreover, several mild yet more common side effects have been noted such as nausea, dizziness, and headaches (Naughton et al., 2013). Nonetheless, data from anesthetic use demonstrate that ketamine's overall risks in the clinical setting are minimal.

As previously noted, research on recreational users has provided some insight on the potentially long-term and adverse side effects of ketamine use. For example, Shahani, Streutker, Dickson, and Stewart (2007) reported that ketamine abusers may develop lower urinary tract problems. Nine daily users of ketamine who presented with hematuria (blood in the urine), severe urinary frequency, urgency and dysuria (painful urination) all showed marked signs of severe urinary tract inflammation, including thickening of the bladder wall and perivesicular stranding (indicating inflammation of the tissue). Thus, chronic, long-term ketamine use can potentially lead to severe ulcerative cystitis (Shahani,

Streutker, Dickson, & Stewart, 2007). This finding was observed in recreational users who were ingesting over 1 gram per day of ketamine over a significant period of time.

According to Jansen (2004), repeated insufflation of ketamine may also damage the lining of the nose or sense of smell. Recreational users have also reported side effects related to the eyes such as blurred, double, or slipping vision or unusual eye movements. Other physical side effects noted by recreational users at moderate doses include slurred speech, rapid breathing, dizziness, numbness, and sweating. Falling, collapsing, and other behavioral effects are also potential risks when ketamine is ingested in uncontrolled settings (Jansen, 2004).

In addition to these physical side effects, the risk of an emergence reaction or psychedelic experience is, of course, an issue with ketamine. To some medical professionals, an altered psychological state or dissociative reaction in response to a drug, even if described as pleasant by the patient, is considered a risk. According to another source from the anesthesia literature, the incidence rate of emergence reactions postanesthetic doses is roughly 10% to 30% (Kumar, n.d.). Patients who have these side effects may experience proprioceptive, auditory, and visual illusions or delirium. Extracorporeal experiences marked by confusion, euphoria, or fear are also possible. These postoperative side effects typically dissipate within 1 hr (Kumar, n.d.). Certain factors increase the likelihood of emergence reactions. Patients between ages 15 and 60 years, female patients, and those with histories of personality disorders are thought to be more susceptible to this risk (Kumar, n.d.). It also has been noted that psychotomimetic side effects are more likely at doses higher than 2mg/kg and when ketamine is administered rapidly (Kumar, n.d.).

An additional ketamine-related risk is known as the "K-hole." This refers to the unintended dissociative experience encountered by recreational users in which one becomes nonresponsive to external stimuli (Jansen, 2004). If the user is not expecting this to happen, it can be quite frightening as the user might not be able to communicate with friends, or, even worse, might be unable to maintain balance and fall over. This phenomenon can also be frightening to those witnessing the experience if they are unable to get the user to indicate that he or she is okay. However, if one is prepared for the K-hole (e.g., lying down in a quiet place with a trained guide) it can be a very pleasant experience (Jansen, 2004). K-holes have been described as "vivid traveling through a world meticulously created in our minds" (Jansen, 2004, p. 169). Recreational users who are brought into emergency departments in a K-hole are often treated with a small dose of a short-acting barbiturate to curtail this reaction (DailyMed.com, 2013).

While data are still emerging, thus far there appears to be very limited clinical risk associated with ketamine use at therapeutic doses. Depressed patients appear to show similar tolerance and safety profiles, particularly in terms of the possible risk of psychosis as a side effect, to healthy, nondepressed patients (Krystal et al., 2013). Although, as previously noted, the safety profile of a single administration or short-term, one-time use of ketamine at an anesthetic dose has been strongly demonstrated, the safety of long-term repeated doses, particularly at subanesthetic levels, is less well known (Naughton et al., 2013). While Zarate et al. (2006) did demonstrate that adverse effects to repeated doses, such as confusion, elevated blood pressure, euphoria, and perceptual disturbances, were slightly more common in participants receiving ketamine than those receiving placebo, no studies focusing on the safety of repeated doses in depressed patients have been done.

In most studies, a relatively low percentage of participants report dissociative symptoms, typically below 20% (Naughton et al., 2013), and these effects resolve within 2 hr.

It should be noted that while information on potential risks and side effects is widely available, what is less established is precisely at what dose these side effects are thought to occur. While different doses of ketamine are used to achieve different effects, side effects are at times generalized to all usage and doses although it is clear that the amount of ketamine administered affects the likelihood of certain associated hazards. Clearer data on the dose at which side effects occur are needed.

Ketamine's Legal Status

Recent clinical trials have shown tremendous promise for a new application of ketamine: for therapeutic purposes. Early clinical evidence supports that low doses of ketamine have fast-acting antidepressant effects for patients with MDD, bipolar disorder, and suicidal ideation (Naughton et al., 2013). Currently, the FDA has approved ketamine for anesthetic and analgesic purposes only. The DEA, which is primarily concerned with controlling the trafficking and distribution of illicit drugs, placed ketamine in Schedule III-N at the federal level in August 1999 (Jansen, 2004). The DEA categorizes controlled substances by assigning a value from I to V, with the lower end of the range including drugs that have low medicinal value and high potential for abuse and the higher end of the range including drugs that have high medicinal value and less potential for abuse (U.S. Drug Enforcement Administration, n.d.). Schedule III is the category of drugs that have a legitimate medical use but less potential for abuse or addiction than Schedule I and II drugs (U.S. Drug Enforcement Administration, n.d., VandenBos, 2007).

Additionally, the N attached to ketamine's DEA designation indicates that it is a nonnarcotic (U.S. Drug Enforcement Administration, n.d.).

It should be noted that while ketamine is not yet FDA approved for therapeutic purposes, this does not mean that this type of use is illegal. Off-label use, or the use of a drug as a treatment for an unapproved indication, dosage, form of administration, or patient population, is legal in the United States. If a medicine is FDA approved for one use, physicians may prescribe it for other purposes if they professionally judge this use as effective and safe (Stafford, 2008). This happens very frequently in the practice of psychiatry, for example, when medications that are FDA approved for treating depression are prescribed for treating anxiety, medications that are FDA approved as antipsychotics are used for treating depression, and medications that are approved as anxiolytics are used for treating psychotic disorders, and so on (G. Greenberg, personal communication, 2011). In addition, physicians may prescribe a drug treatment even if its approved usage falls outside of their area of medical specialization. As long as physicians are registered with the DEA and have the appropriate schedule allowance for the controlled substance that they wish to prescribe, then they are permitted to use their professional judgment to prescribe any medication for any condition (FDA Controlled Substances Act, 1970). In other words, in the United States it is at a physician's discretion to prescribe the best treatment or medication, especially in cases where standard treatment or treatments have failed.

There have been numerous examples of the use of non-FDA approved medications when the situation warrants such use. (To reiterate: Ketamine is legal and FDA approved for anesthetic and analgesic applications as previously stated, but it is not

yet approved for antidepressant purposes.) During the time that the present study was being completed, an example of a non-FDA approved medication was prominently in the news. In late 2013, there was a serious outbreak of meningitis at Princeton University during which seven students contracted the illness before government health officials stepped in. The Centers for Disease Control finally made the recommendation that the residential students at Princeton be administered Bexsero, a non-FDA approved vaccination for the strain of meningitis that was circulating in their community. In its recommendation, the agency stated that in matters of serious illness or potential death urgent clinical treatment needs takes precedence over the need to complete the FDA approval process (Aleccia, 2013).

Routes of Administration

Similar to its use for anesthetic and recreational purposes, there are various routes of administration available for ketamine's therapeutic uses. In addition to the common IV route, ketamine can also be given as an IM injection, and it can be absorbed rectally, nasally, sublingually (under the tongue), and orally (Stevenson, 2005). Non-IV routes of administration are currently being tested in depressed populations, and several are considered to be hopeful possibilities for therapeutic use (Krystal et al., 2013).

Most of the clinical studies completed thus far have administered ketamine via IV. Being able to adjust the rate of the drip is the advantage of this administration approach, which is often done in medical settings to control its effects and longevity. However, ketamine delivered by IV requires the longest visit to the medical facility as well as constant monitoring throughout administration. It also is the most expensive and elaborate setup, requiring the most skill on the provider's part.

Alternate routes of administration of ketamine have been increasingly explored. IM injection is frequently used in treating children for medical procedures and is also used to administer ketamine for analgesic purposes (Stevenson, 2005). The bioavailability of the IM route is 93% (Kumar, n.d.). In addition to its ease of administration, IM-injectable doses of ketamine are also extremely inexpensive, currently about $9 for a vial of 500 mg or roughly $1.80 per treatment. However, IM injection may not be the best choice for drug naïve patients because the treatment cannot be slowed down or stopped if needed as it can be with IV administration.

If it could be demonstrated to achieve significant efficacy, oral administration would be a desirable option given its ease of use and its potential for at-home administration. However, the efficacy of oral ketamine for antidepressant purposes has not been firmly established as some research has indicated that oral ketamine is actually less effective at producing an antidepressant effect than other routes of administration (Cusin, Hilton, Nierenberg, & Fava, 2012). The bioavailability of orally administered ketamine is around 20% (Kumar, n.d.) as compared with 93% of ketamine given IM (Cusin et al., 2012), so larger amounts of ketamine need to be ingested. Also, oral ketamine also appears to take longer to reach effectiveness, which makes intuitive sense given that it has to pass through the digestion system before reaching the CNS. Nonetheless, researchers are hopeful that some form of oral ketamine will be useful in the future, perhaps to extend the efficacy of an IM or IV ketamine treatment (Krystal et al., 2013).

One recent study showed that oral ketamine was clinically useful for a small group of patients who were experiencing depression, anxiety, and pain. Irwin et al.

(2013) used an open-label study design (where the subjects knew what medicine they would be getting) with 14 patients receiving hospice care who were also experiencing significant depression. The subjects received daily oral doses (0.5 mg/kg) of ketamine for 28 days. Symptoms of depression and anxiety, as measured by the Hospital Anxiety and Depression Scale, were reduced significantly for the eight patients who completed the trial. (Four patients withdrew from the trial due to no response to the ketamine and two withdrew for unrelated medical health problems.) Ketamine-associated side effects were minimal and included trouble sleeping, agitation, and/or diarrhea; but, interestingly, psychogenic side effects were not noted. While this study lacked the robustness of a study using a control group or a randomized design, it nonetheless opens the door to further study of oral ketamine for depression.

Intranasal administration of ketamine for therapeutic purposes is still being investigated, and studies on its efficacy for patients with depression are lacking. As of this writing, there were two studies on this approach underway that were expected to be published later in 2014. However, research has demonstrated ketamine's effectiveness for significantly relieving pain in chronic pain patients (Naughton et al., 2013), which suggests that intranasal administration might be able to achieve some sort of therapeutic effect. However, according to recreational users snorting ketamine produces a noticeably less intense psychedelic experience than IM administration (Turner, 1994), so intranasal administration may not be the most efficacious. Further research is needed.

Lastly, ketamine may also be administered transdermally, a route of administration utilized for localized analgesic purposes. A mixture of 10% ketoprofen, 5% lidocaine, and 10% ketamine is commonly used (Kumar, n.d.). It is unclear if this is

a potential avenue for achieving an antidepressant effect via ketamine administration, and no research has been done on this thus far.

Ketamine-Assisted Psychotherapy

Prior to the realization that ketamine produces a rapid acting and specific antidepressant effect, it was explored as an adjunct to psychotherapy. Used in this way, ketamine was valued for its psychedelic, egolytic, or hallucinogenic properties.

One of the first psychotherapists to use ketamine therapeutically was Salvador Roquet, a psychiatrist and psychoanalyst. In the 1960s, Roquet traveled and studied extensively with the native healers of Mexico who influenced his thinking about the ritual use of psychedelic medicines in a healing context. He developed a new and controversial form of treatment that he called "psychosynthesis," which combined elements of psychoanalysis and psychedelic mind exploration (Yensen, 1973). According to Yensen (1973), Roquet conducted psychosynthesis as a group session that included deliberate sensory overload created by simultaneously playing multiple movies and music. At the same time, Roquet and his assistants administered a psychedelic agent that sometimes included ketamine to the participants. During this active phase of treatment, participants were encouraged to open up to new ways of thinking about their difficulties. Later, after participants had a chance to rest, the group discussed the participants' thoughts and insights (Yensen, 1973). Roquet felt that 10 to 20 drug sessions were needed to see substantive change in a person, but he reported success in treating a variety of patients including neurotics, people with personality disorders, and schizophrenics with this method. Roquet believed this approach allowed for a profound reorganization of the personality to occur through the combined use of sensory stimulation and a psychedelic

agent, which together disrupted the normal functioning of the defense mechanisms and permitted access to the deeper self (Yensen, 1973).

In the 1970s, Iranian psychiatrists began exploring ketamine as an adjunct to psychotherapy with a variety of patients. They felt that the addition of ketamine greatly enhanced their treatment outcomes, and they published many papers on their findings in several languages (Khorramzadeh, as cited in Sewell, 2007).

In the 1998, a British team found that by combining ketamine with an opioid blocker (to prevent loss of consciousness) relieved patients with highly refractory anorexia nervosa of their compulsive thoughts and behaviors on a temporary basis (Mills, Park, Manara, & Merriman, 1998). The 15 female patients in this study each received 20 mgs of ketamine per hr for 10 hr along with nalmefene (the opioid blocker). Nine patients showed prolonged remission when additional ketamine infusions were given (Mills et al., 1998). The study authors did not clearly indicate whether the clinicians were using ketamine primarily as a therapeutic catalyst or a chemical agent.

According to Kolp et al. (2007), during the 1990s and early 2000s a tremendous amount of research on using ketamine to treat addictions was done in Russia. Much of it was overseen by a psychiatrist named Evgeny Krupitsky, who currently lives and works in the United States. Krupitsky developed a technique called ketamine psychedelic therapy (KPT) for the treatment of addictions that combines individual psychotherapy, group therapy, aversive conditioning, and psychedelic (ketamine) treatment. In one of Krupitsky's studies, the KPT method was used to treat 111 male alcoholics during a 3-month in-patient treatment program (Kolp et al., 2007). All subjects participated voluntarily in the treatment program and gave informed written consent to be in the KPT

study. The control group was composed of 100 male alcoholics of similar ages and backgrounds. These patients underwent the same 3-month treatment course at the same hospital but received only conventional treatments. To determine treatment efficacy, researchers collected follow-up information on all patients 1 year after the end of their treatment (Kolp et al., 2007).

According to Kolp et al. (2007), the researchers found that the abstinence rate was 66% for individuals in the KPT group as compared with 24% in the control group. Thus, they concluded that KPT increased the efficacy of treatment for alcoholism. Further, follow-up data collected at the two-year and three-year mark showed higher rates of sobriety among patients who had received KPT as compared with patients who did not receive KPT, and several patients who received KPT stated to researchers that they had vivid memories of their ketamine sessions which left lasting impressions on them (Kolp et al., 2007).

Krupitsky went on to treat over 1,000 patients with addictions and other psychological disorders using KPT (Kolp et al., 2007). Through a series of controlled clinical trials, he concluded that KPT is safe and effective for treating addictions to alcohol, heroin, ephedrine, posttraumatic stress disorder, depression, and neurotic difficulties (Kolp et al., 2007). Krupitsky also reported that KPT was somewhat helpful but less effective in treating phobias, obsessive-compulsive disorder (OCD), and prominent personality disorders (Kolp et al., 2007). Russian restrictions on ketamine use outside of anesthesia in the early 2000s brought Krupitsky's pioneering research to a halt, and he immigrated to the United States to continue his work (Kolp et al., 2007).

Eli Kolp, an American psychiatrist in private practice, published two case studies on using ketamine to ease anxiety in two patients living with terminal cancer diagnoses. He chose ketamine for these patients because of its unique ability to induce near-death experience, its tendency to be euphoric and well tolerated, its relative safety, and its short duration of action (Kolp et al., 2007). Kolp meet with each patient several times before and after the ketamine session to create a sense of a working relationship, to clarify expectations, and to process the experience together. He reported that one patient felt she had a profoundly helpful experience that greatly reduced her anxiety about dying whereas the other patient seemed minimally helped by the single ketamine session (Kolp et al., 2007). Nonetheless, Kolp described a model for how ketamine could be used and thought about as an adjunct to a therapeutic process.

Clinical Research on Ketamine

It is only within the last 8 years that ketamine has moved away from being considered a highly unorthodox treatment and into the spotlight as a potential new tool for treating several major mental health concerns. At this point, the discussion turns to recent experimental research and the disorders that are a primary focus of attention: depression, bipolar disorder, and suicidality.

MDD

Patients with depression actually comprise several mood-related disorders, including MDD and persistent depressive disorder (formerly known as dysthymic disorder). According to the *DSM–5*, a patient with MDD must have two or more major depressive episodes (APA, 2013). The diagnostic criteria include a depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks as well as at least

five symptoms present, which may be related to energy levels, interest, appetite, and mood (APA, 2013). To be considered unipolar depression, these moods may never appear in conjunction with manic moods. Persistent dysthymic disorder is marked by a regularly depressed mood for at least 2 years for adults as well as two or more symptoms such as fatigue, insomnia, and hopelessness that cause impairment to one's normal functioning (APA, 2013).

Depression has severe psychological and physical consequences for those who suffer from the disorder. Worldwide, 6.6% of the general population is affected by MDD in any given year and 16.2% of the population is affected by it at some point in their lifetime (Coppola & Mondola, 2012). Depression is also twice as common in women as it is in men (Coppola & Mondola, 2012).

Despite depression's prevalence and that the rate of antidepressant use rose by 400% from 1998 to 2008, existing pharmacotherapies for depression have notably limited effectiveness (Chiaet, 2013; Krystal et al., 2013). The majority of antidepressants, which act as serotonin reuptake inhibitors, begin their mechanism of action in the body rather rapidly yet they typically take a long time (3 to 6 weeks) to reach efficacy for reasons that are still unknown (Chiaet, 2013). The fact that it can take several weeks for patients to begin experiencing relief from depressive symptoms is obviously problematic for severely depressed or suicidal patients (Chiaet, 2013). Additionally, while currently available pharmacological treatments do relieve depressive symptoms for many patients, less than one third are able to fully achieve remission after trying one antidepressant medication and less than two thirds are able to achieve remission after trying multiple medications (Coppola & Mondola, 2012). Further, most patients experience one or more

unpleasant side effects from antidepressant medications, which may include nausea/vomiting/digestive distress, drowsiness, headaches, sexual dysfunction, dizziness, weight gain, and/or an increase in suicidal ideation, among others (National Institute of Mental Health, 2013).

Those who are not helped by standard antidepressant treatments such as pharmacotherapy and psychotherapy are referred to as "treatment-resistant" or refractory patients. However, there is no general consensus on the definition of treatment-resistant depression (Krystal et al., 2013). Nonetheless, the literature noted widespread observations of certain depressed patients who fail to respond to normal courses of treatments or medication. Generally, a treatment-resistant patient is regarded as having no or inadequate response to multiple attempts at treatment, sometimes formally measured in clinical settings as a nonpositive response on the Hamilton Rating Scale for Depression (Krystal et al., 2013). There is also a lack of consensus regarding what to call the many patients who receive some benefit from pharmacological interventions but who find the many side effects intolerable, rendering the treatment nonviable. These patients are also sometimes included in the group of patients who are considered treatment-resistant although this designation is usually reserved for patients who fail to respond to medications or for whom a combination of medications, talk therapy and/or electro-convulsive therapy (ECT) does not produce sufficient improvement in symptom relief and/or functioning.

Ketamine for Depressed Patients

Recent research demonstrates that, as predicted by animal models, ketamine may be a breakthrough solution to the current challenge of slow-acting and low-efficacy

pharmacological treatments for depression. Low to moderate doses of ketamine appear to be effective for producing exceptionally rapid antidepressant effects in patients with MDD, particularly in those who are treatment-resistant and have not responded to conventional medications or ECT (Krystal et al., 2013).

Arguably the first clinical study to demonstrate ketamine's rapid antidepressant effects was a randomized, placebo-controlled, double-blind study on seven subjects conducted by Berman et al. in 2000. Each subject received both a single infusion of IV ketamine (.5 mg/kg) and inactive saline solution at different times, but neither the subjects nor the researchers knew which condition the subjects had received. Originally nine subjects were selected for this study, including four men and five women. Two subjects identified as Hispanic and seven identified as White. There were no African American or Asian subjects. The mean age was 37 years with their actual ages ranging from 23 to 55 years. All subjects met the criteria for currently experiencing an MDD; eight were diagnosed with MDD and one had bipolar disorder (type not specified). One subject had a current comorbid diagnosis of panic disorder but no other subjects had any other comorbid diagnoses on Axis 1. Two subjects had previous histories of alcohol abuse (in remission for 8 years or more), and no subject had a current history of substance abuse. All subjects were judged to be in good physical health, free of substances, and off of any medications for a 2-week period prior to the start of the study (Berman et al., 2000). Two subjects left the study prematurely in order to pursue other antidepressant therapies, leaving seven subjects to complete the study.

Berman et al. (2000) assessed depressive symptoms using the Hamilton Depression Rating Scale and the Beck Depression Inventory, and they assessed

psychotomimetic symptoms using the Visual Analog Scales for Intoxication and the Brief Psychiatric Rating Scale (BPRS) with a special interest in the "positive" symptom items. Subjects were tested at baseline, at 80 and 230 min, and at 24, 48, and 72 hr postadministration.

Berman et al. (2000) found a very significant improvement in all subjects' depressive symptoms within 72 hr after receiving the ketamine treatment but not after receiving the inactive treatment. In fact, there was a 50% or greater decrease in the Hamilton Depression Rating Scale scores for four of the patients, which is an astounding result. Although the sample size was extremely small, Berman et al. noted that there was statistically significant improvement in several specific symptom domains, namely suicidality, helplessness, and feelings of worthlessness. They also noted that increases in the Visual Analog Scales for Intoxication and the positive symptom scale of the PBRS that peaked around 110 but that did not appear to be problematic or distressing for any of the subjects. Berman et al. also reported that the antidepressant effect of the ketamine treatment lasted 1 to 2 weeks following the infusion, but how they determined this was unclear.

The strengths of the Berman et al. study (2000) include its randomized and double-blind design and its use of a control condition. The study was further strengthened by using more than one tool to measure depression and by the researchers' interest in ketamine treatment's psychogenic effects. The study's major weakness is its small sample size, although this is not unusual for a pilot study, and the fact that two of the original nine subjects left the study prematurely, possibly biasing the findings. Another concern is the fact that subjects were required the be off of medications for 2

weeks prior to the study, which raises the questions of if Berman et al. recruited subjects who were not taking medications or did they consider the impact of taking patients off of their medications? The implications of these questions were not discussed. Further, Berman et al. stated that the subjects were assessed at 72 hr posttreatment but returned to their baseline levels of depression after 1 to 2 weeks. What exactly happened during this period? The study would have been strengthened if this had been clarified. Nevertheless, this groundbreaking study paved the way for future research on ketamine as a rapid-acting antidepressant.

Another hint at ketamine's antidepressant effects came from the anesthesia field. Kudoh, Takahira, Katagai and Takazawa (2002) did a controlled, randomized study of 70 patients who were undergoing orthopedic surgeries. They identified patients who met the criteria for a depressive episode at the time of their surgery. In this study, one group of patients received ketamine as part of their anesthetic medicant and two control groups received other kinds of anesthesia. The researchers found that the patients who received ketamine demonstrated less postoperative depression and pain than patients who received other anesthetics. Subjects in the ketamine group specifically showed a significant reduction in depressed mood, suicidality, anxiety, and hypochondriasis compared with patients in the two control groups.

In 2006, Zarate et al. sought to replicate Berman et al.'s 2000 findings in a new study. In Zarate et al.'s randomized, placebo-controlled, double-blind, crossover study (meaning that all subjects experienced both conditions, but they did not know which condition they were experiencing at the time), 18 treatment-resistant patients with long histories of MDD were carefully selected as participants. Study subjects were 12 women

and 6 men who ranged from 19 to 62 years of age, and the average length of their depressive illness was over 23 years (actual range was 3 to 47 years). The average number of medications each subject had tried without success was five, plus some had tried ECT. Their racial and ethnic identities were not published, and their sexual orientations were also not published. Zarate et al. noted that the subjects were selected for the severity and treatment-resistance of their depression and that these findings might not be generalizable to other populations.

After a 2-week drug-free period, each subject was given both an intravenous ketamine treatment (0.5 mg/kg) and an inactive treatment of saline solution 1 week apart (Zarate et al., 2006). Subjects were rated at baseline and at 40, 80, 110, and 230 min and again on Days 1, 2, 3, and 7 postinfusion using measures for depression and psychogenic features. Zarate et al. (2006) reported that when the subjects received ketamine they showed a very significant improvement in their depressive symptoms, most prominently at 110 min postinfusion, and this effect remained substantial throughout the following week.

In another recent study, Carlson et al. (2013) sought not only to confirm ketamine's effectiveness in producing antidepressant effects for patients with MDD but to also determine the related mechanisms that occur within the brain by looking at the brain's metabolic processes before and after ketamine administration. Twenty patients with treatment-resistant MDD were given a single dose of 0.5 mg/kg of ketamine. Metabolic data was measured via positron emission tomography (PET) scan prior to and after infusion. The results showed that the relief of depressive symptoms was positively correlated to metabolic changes within the right superior and middle temporal gyri. In

other words, treatment-resistant patients with MDD demonstrated decreased metabolism in specific prefrontal areas when rapid antidepressant effects were occurring (Carlson et al., 2013). Notably, Carlson et al. also observed stimulation in sensory association cortices, most likely related to the dissociative and hallucinatory side effects associated with ketamine. In addition, out of the 20 subjects, 30% achieved a significant (over 50%) reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) score and were considered to be positive responders to ketamine (Carlson et al., 2013). This study was the first of its kind to establish the anatomical correlates of ketamine's antidepressant effects. However, participants only received a single dose of ketamine, the sample size was small, and there was no placebo group. In addition, the percent of significant responders (30%) was markedly lower than what previous studies had found. Carlson et al. speculated that this may have been because all of the participants were severely treatment-resistant according to the criteria established for the study..

In the largest study on ketamine's use for depression to date, Murrough et al. (2013) compared the effects of a single ketamine dose to a single dose of midazolam, a sedating benzodiazepine with some mild psychoactive properties. The purposes of this study were to (a) test the effectiveness of ketamine in a larger subject group; and (b) to test ketamine against an active control to enhance the methodological rigor of a double-blind experimental design (Murrough et al., 2013). This study used a randomized, double-blind, between-groups controlled design. The subject group consisted of 72 patients diagnosed with MDD who were experiencing a depressive episode. Murrough et al. noted that virtually all of the subjects had early onset depressive illnesses and that their symptoms were generally moderate to severe. Exclusion criteria were any

indication of a psychotic disorder, bipolar disorder, substance abuse within the last 2 years, current medical illness, suicidal risk as defined by the researchers, and the inability or unwillingness to tolerate a medication wash-out period for 2 weeks prior to the beginning of this study. A table in the article included information on gender, ethnicity, marital status, education level, number of previous suicide attempts and so on for the subjects although this information was not discussed in the body of the article.

Murrough et al. (2013) randomly assigned patients to an experimental or control group. Those in the experimental condition received 0.5 mg/kg ketamine by IV and those in the control condition received 0.045 mg/kg of midazolam by IV. The subjects were assessed using the MADRS and several additional measures, including the Clinical Global Impression Scale. The researchers also noted adverse effects and used the Dissociative States Scale and the BPRS to measure psychomimetic effects. Subjects were monitored continuously throughout infusion and again at 24, 48, 72 hr and 7 days postinfusion. Some subjects were followed for up to 4 additional weeks if they continued to show a positive response to treatment (Murrough et al., 2013).

The results of the Murrough et al. (2013) study showed that the subjects in the ketamine group had a greater improvement in their MADRS scores than the subjects in the midazolam group 24 hr after treatment and that several subjects in the ketamine group still met the criteria for a positive response on Day 7, but all patients eventually relapsed to their pretreatment state. There were also some reported side effects in the patients who received ketamine, including dizziness, headache, nausea, and restlessness. In addition, eight subjects who received ketamine reported having some "dissociative" symptoms that Murrough et al. defined as "feeling outside one's body" or time distortion. However, no

subjects had “psychotic” symptoms, which Murrough et al. defined as hallucinations, paranoia, or thought disorders. Also, two subjects who received ketamine experienced changes in blood pressure, which was of concern but which resolved (Murrough et al., 2013).

The strengths of the Murrough et al. (2013) study were the larger subject group and the use of an active placebo control group. Murrough et al. commented that the ethnic and racial diversity of the subject group enhanced the reliability of the findings. They added that the observed psychoactive and hemodynamic effects were consistent with what was previously known about ketamine. They also made it a point to say that there was no evidence that ketamine treatment caused psychotic or manic symptoms in any subject during the study’s follow-up period. Finally, Murrough et al. noted that although their study supported previous findings that ketamine may be useful as a short-term adjunctive therapy for acute depression, it did not address questions related to ketamine’s safety or efficacy as an ongoing treatment.

Several recent studies have focused on repeated infusions, administered on alternate days over an extended period of time, in an attempt to extend ketamine’s effects and investigate the efficacy of multiple doses rather than a single dose. Collins et al. (2010) investigated repeated ketamine infusions in 10 patients. If patients demonstrated a positive response on Day 2 as evidenced by a 50% or greater reduction in MADRS score, they then received five additional doses on an every-other-day schedule. Nine patients qualified to receive the extended doses, yet all nine relapsed approximately 19 days or less after the last infusion. This study’s limitations should be noted: its sample size was small and there was no control group. It should also be noted that this study, as well as

others that aim to test the efficacy of repeated doses, typically are designed so that repeated doses are only administered to those who show a positive response to the initial ketamine dose, leaving it unclear if patients who fail to respond to the initial treatment should be given further treatments.

One exception to this trend is Murrough et al.'s (2012) study in which the researchers originally intended to have a similar study design but later opted to instead administer repeated doses of ketamine to all participants, even those who did not demonstrate significant response to the first dose. Murrough et al. attempted to determine the pattern and durability of the antidepressant effects in repeat doses with a larger sample of 24 treatment-resistant patients with MDD. Subjects received six open-label IV infusions of ketamine at 0.5 mg/kg three times per week over a period of 12 days (Murrough et al., 2012). As indicated by improvements in their MADRS scores, 71% of patients had a positive response. Antidepressant effects were observed as quickly as 2 hr postinfusion and were generally sustained over the course of the repeated doses. Additionally, Murrough et al. made it a point to measure dissociative and psychotomimetic effects and found that subjects showed a small yet significant increase in these kinds of experiences. These symptoms, described as "feeling strange or unreal, abnormal sensations, blurred vision, and feeling drowsy or sleepy," (p. 254) generally resolved completely within 4 hr after administration (Murrough et al., 2012.

While continuing treatments even if patients did not show a good response to the initial dose was a noted strength of the study, Murrough et al. (2012) found that the response to the first dose was actually a strong indicator and highly predictive of patients' response to subsequent doses with 94% sensitivity and 71% specificity. Interestingly,

suicidal ideation was also observed as sharply decreasing in all participants, even those whose overall MADRS score reduction did not qualify as significant enough to be counted as an overall positive response to ketamine.

It should be noted that similar to other studies' findings, Murrough et al. (2012) found that most participants relapsed within 1 month after their final dose of ketamine. So, although the antidepressant effect can be rapid and robust, it is not long lasting. Nonetheless, Murrough et al. and other studies do show that ketamine's antidepressant effects are sustained throughout the duration of the subsequent doses, despite that these effects generally dissipate generally 2 weeks to 1 month after the final infusion. This points to ketamine's potential effectiveness as a short-term antidepressant remedy for those patients waiting for other interventions to take effect.

Bipolar Disorder

Bipolar disorder includes bipolar I, marked by periods of both depression and mania, and bipolar II, marked by periods of both depression and hypomania (APA, 2013). Hypomania is similar to mania but less severe and not resulting in hospitalization, breaks with reality, or profound impairment to normal day-to-day functioning. The diagnostic criteria for a major depressive episode in the course of bipolar illness are the same as those for MDD, and the criteria for a manic episode include a period of a least 1 week with an elevated or expansive mood marked by symptoms such as reduced sleep, risky behavior, and inflated self-esteem that lead to social or occupational impairment (APA, 2013). Bipolar disorder has similar rates of prevalence among males and females although gender does appear to influence the frequency and cycling of episodes. The prevalence of the bipolar disorders in the worldwide population is often thought to be

around 2% (National Institute of Mental Health, 2013), but other researchers believe that the number might be as high as 4% (T. Ketter, personal communication, July 2012).

Similar to MDD, many patients with bipolar disorder respond poorly to existing drug therapies (Coppola & Mondola, 2012). Bipolar disorder is notoriously difficult to treat. While manic episodes generally respond well to medications (if the patients are willing to comply with the medication regimen and if the side effects are tolerable), depressive episodes are extremely difficult to treat because most antidepressants run the risk of inducing mania or mood cycling in bipolar patients (Krystal, 2013). Even when standard pharmacotherapy shows some efficacy, side effects, residual depression, and cognitive deficits often continue to be problematic (Coppola & Mondola, 2012). In contrast to traditional pharmacological treatments, it has been found that low doses of ketamine do not induce an affective switch, making it a particularly attractive treatment option for this population (Naughton et al., 2013).

Ketamine for Bipolar Patients

In a follow-up to their previous study that showed ketamine's robust and rapid antidepressant effects for patients with MDD, Zarate et al. (2012) conducted a double-blind, randomized, crossover, placebo-controlled study of 15 subjects with bipolar disorder (type I or II) who were currently experiencing a depressive episode. The researchers administered 0.5 mg/kg of a single infusion of ketamine to the subjects who were currently taking lithium or valproate (Depakote) as a mood stabilizer. Using the MADRS to measure depressive systems, the test was given at baseline and 40, 80, 110, and 240 min after the single infusion as well as 2 weeks later. Within 40 min, depressive symptoms and suicidal ideation were significantly reduced in those who received

ketamine compared with placebo (Zarate et al., 2012). This effect remained significant for 3 days, and subjects demonstrated similar rates of response to those with MDD: 79% responded positively to ketamine and 0% responded positively to placebo (Zarate et al., 2012). In essence, this replicated the results of Zarate et al.'s 2006 study on patients with MDD. Specifically, both of Zarate et al. studies found that in depressed and bipolar patients, ketamine had a similar rapid onset (40 min), similar response rates, and similar duration. Zarate et al. (2012) also noted in this study that the most common side effect reported was dissociative symptoms, which tended to be brief and occurred most frequently at the 40-min mark.

The study's double-blind, placebo-controlled, and randomized design was a noted strength (Zarate et al., 2012). However, the small sample size of patients with very long and complicated treatment histories, including some who had past ECT treatment, are limitations. Zarate et al. (2012) further noted that although studying ketamine's efficacy for treatment-resistant patients has been a major area of interest, the results of this study may not be generalizable to other depressed or bipolar patients.

Cusin et al.'s (2012) study that investigated ketamine's long-term efficacy in two subjects is also notable here because it looked at various routes of administration and flexible dosing parameters over long periods of time in two highly refractory patients with bipolar II disorder. Patient 1 presented with attention-deficit hyperactivity disorder in addition to bipolar II as well as depressive episodes that did not respond to conventional medications or ECT (Cusin et al., 2012). Interestingly, although this patient did not respond to the initial ketamine dose, she began showing significant response after the third injection. First, she was given 0.5 mg/kg of ketamine via IM injection twice per

week for a total of five times. When her depressive symptoms returned 10 days after the fifth infusion, various other routes and doses were attempted, all without success: 210 mg of oral ketamine three times per week, then 200 mg/mL of intranasal ketamine three times per week, and then 32 mg of ketamine via IM injection. Finally, when her dose was increased to 50 mg of ketamine administered via IM on a set schedule of every 4 days, she achieved complete remission for several months. Patient 1 did experience negative side effects of nightmares and dissociation at one point in her treatment although not to the extent that the dose needed to be adjusted (Cusin et al., 2012).

Patient 2 presented with bipolar II disorder, attention-deficit hyperactivity disorder, chronic depression, and suicidal ideation (Cusin et al., 2012). This patient was also described as treatment resistant. The patient did not respond to the original dose of 150 mg of oral ketamine three times per week. Next, 100 mg of ketamine via IM injection was attempted, but the patient was unable to tolerate the dissociative side effects. When the dosage was reduced to 50 mg every 3 days, she was able to tolerate it well and showed complete resolution of suicidal ideation and improvement to her depressive symptoms although not full remission (Cusin et al., 2012).

Taken together, these case studies study illustrate the point that there is no one-size-fits-all approach for ketamine treatment. Instead, the treatment team and the patient need to work together to find the threshold at which therapeutic relief is experienced and where the side effects are tolerable, and this can vary a great deal among individual patients.

Suicidality

Historically, suicidal ideation did not have its own separate diagnostic category although it was considered for a new one in the *DSM–5* (APA, 2013, p. 801). It is most often seen as comorbid with other diagnoses, especially mood disorders, but it may also be present in patients with substance abuse, anxiety disorders, thought disorders such as schizophrenia, and/or personality disorders (APA, 2013).

A pressing public health issue, suicide is the third-leading cause of death for individuals ages 15 to 24 years (Caruso, n.d.). In the United States, each year there are approximately 11 suicides per 100,000 people and 1.3% of these deaths are due to suicide (Caruso, n.d.). These numbers include completed suicide attempts only; the number of attempted suicides, including uncompleted attempts, is even more staggering with over 800,000 suicide attempts in the United States alone in 2005 (Caruso, n.d.). By age group, the highest rates of suicide in the United States occur in those over 20 years of age with the highest rate occurring for the age bracket of 85 years and older at 17 suicides per 100,000 (Caruso, n.d.). Although females attempt suicide more frequently than males with three times as many attempts by females as compared with males, male suicide attempts more frequently end in a completed suicide. Of all completed suicides in the United States, 73% were done by White males (Caruso, n.d.). On a global scale, over 1,000,000 people commit suicide each year (Caruso, n.d.). Worldwide, the global suicide rate is 16 suicides per 100,000. Interestingly (and sadly), the recorded rate has increased 60% over the past 45 years (Caruso, n.d.) although the precise reasons for this phenomenon are not well understood.

In addition, a large number of patients present to emergency rooms across the United States each year with suicidal ideation or after attempts of self-harm—713,000 in 2010 alone (CDC, 2013). However, there is no known single efficacious intervention or treatment for these patients, given that suicidal ideation may be related to a wide range of comorbid disorders or causes (Caruso, n.d.). Thus, suicidal patients comprise their own special subgroup because when they present to an emergency room their entire diagnosis may be unknown. Further, due to the range of possible comorbid disorders, selecting a single medication to relieve suicidal thoughts is a notable challenge, and the delayed onset of currently available antidepressants is especially problematic for those at risk of suicide (Coppola & Mondola, 2012). Current protocol in emergency room departments is to keep the patient in a controlled environment to prevent self-harm, but this approach is extremely expensive and it fails to address the underlying desire to hurt oneself. Ketamine, with its fast-acting antidepressant effects that appear particularly efficacious for suicidal ideation, is a new potential avenue for helping some of these individuals.

Ketamine for Suicidal Patients

Patients with prominent suicidal ideation were excluded in early clinical trials of ketamine's antidepressant effects. However, some early studies noted that ketamine also significantly reduced suicidal ideation scores on the measures used (Berman et al., 2000; Zarate et al., 2006). Zarate et al. (2012) reproduced this finding in their open-label study that investigated the effects of ketamine on suicidal ideation in bipolar patients. As previously noted, Zarate et al. (2012) was the first controlled study to demonstrate that a single infusion of ketamine produces a measurable, extremely rapid, and robust

antisuicidal effect in patients with bipolar depression, even in those who did not qualify for a positive response to ketamine on other measures of the MADRS scale.

Price, Nock, Charney, and Mathew (2009) looked specifically at the effect of ketamine treatment on suicidal ideation in a small sample of patients with MDD and suicidal thoughts. This study actually consisted of two parts. In the first part, IV ketamine (0.5 mg/kg) was administered to 26 subjects who were experiencing a treatment-resistant episode of depression as defined by two or more unsuccessful attempts to relieve the depressive symptoms with standard antidepressant medicines. The subjects were assessed just prior to and 24 hr following the treatment using several measures: the explicit suicidality item from the MADRS (MADRS-SI), the Beck Scale for Suicidal Ideation, which contains 21 items, and the Implicit Association Test. The researchers argued that the Implicit Association Test could be helpful in revealing patients' true feelings about socially taboo topics such as self-harm and cited evidence for its reliability in predicting future behavior.

As with other studies in this area, the subjects in the Price et al. (2009) study were diagnosed with MDD and had moderate or severe symptoms of depression, they had to be free of medications for a 2-week period before the beginning of the study, they had to be free of a substance abuse problem from at least 6 months, and they had to be in good physical health aside from their depressive illness. Exclusion criteria included a history of a psychotic disorder, mania, or hypomania. Ironically, patients with active suicidal ideation were also excluded.

The results from the first part of the investigation found a very significant decrease in the subjects' suicidal ideation following a single ketamine infusion (Price,

Nock, Charney, & Mathew, 2009). For example, the subjects' score on the MADRS-SI dropped by an average of 2.08 points on a 6-point scale with 81% of patients indicating a rating of 0 or 1 (very low desire to self-harm) at 24 hr postinfusion. Price et al. (2009) also noted decreases in other MADRS scores (on nonsuicide items), leading them to speculate that that ketamine's antisuicidal effects are mediated by overall depression reduction.

In the second part of the study, a subset of 10 patients from the initial study elected to have five more ketamine treatments on an alternate-day regimen. Price et al. (2009) noted that 90% of these subjects rated themselves at 0 on the MADRS-SI following the first infusion during this part of the study (their second infusion overall). The improvement in suicidal ideation was maintained throughout the 12-day period during which the subjects received ketamine with no subject scoring above a 2 on the MADRS-SI item during treatment. Price et al. did not explicitly state but implied that the subjects remitted at some point following cessation of the ketamine infusions.

While this study demonstrated some impressive and promising results, there were several notable weaknesses. First, there was no control group for this study, and the question must be raised regarding the size of a possible placebo effect of attention, structure, and containment on the subjects. Next, the decision to exclude actively suicidal patients from the study and what exactly were the criteria for making this decision could be questioned. In addition, the article made no note of subject demographics, making it hard to know whether the findings are generalizable and reliable. Finally, nothing was said about the physical and/or psychological side effects of the ketamine treatment, which makes the study seem incomplete. Nonetheless, this study reinforces what others have

shown, namely that ketamine has a robust antidepressant and antisuicidal effect that can be sustained (at least in the short term) by repeated treatments.

Larkin and Beautrais (2011) conducted a naturalistic study on using open-label, low-dose ketamine (0.2 mg/kg) for suicidal patients who were brought into the emergency department at a large urban hospital. There were 15 subjects in this study. Once patients were admitted into the study, the MADRS was administered to each subject five times: preinfusion and then at 40, 80, 120 and 240 min postinfusion. Subjects were then contacted over a period of 10 days for follow-ups and were reassessed. Study findings showed that the overall depression scores and the specific scores for suicidal ideation decreased significantly during the 4 hr following the ketamine treatment and that the effect was sustained to a significant degree for 10 days (Larkin & Beautrais, 2011). This small study is especially significant because it was not conducted in an experimental setting but rather explored the use of ketamine in a real-world application.

Although ketamine shows notable capacity for use in emergency room settings to quickly reduce suicidal ideation, many patients who present with suicidality to emergency rooms usually have another psychological disorder that must be taken into consideration, and if the patient's full physical and psychological picture is unknown administering ketamine could be risky. Most clinical trials on ketamine as an antidepressant exclude certain patient populations, including those with histories of psychosis, schizophrenia, or drug dependence. More research is thus necessary on the potential risks of administering ketamine to a patient with suicidal ideation related to disorders other than MDD or bipolar disorder.

In addition, when considering ketamine's use in the emergency room, there is also the risk of providing increased access to ketamine abusers and recreational users. It is necessary to consider the potential for increasing rates of abuse as there reportedly have been unpublished cases of patients with substance abuse histories abusing ketamine after receiving it as an antidepressant (Krystal et al., 2013). However, if ketamine shows exceptional success for the rapid reduction of suicidal ideation, it may be a solution worth exploring given that other efficacious treatments that must be monitored for abuse and used with caution, such as various pain medications, are still widely used in emergency rooms.

Other Therapeutic Uses of Ketamine

In addition to examining its therapeutic effects for patients with depression, bipolar disorder, and suicidality, several additional uses for ketamine are also currently being investigated. Though outside the scope of the present study, they are briefly noted here.

Ketamine is used for analgesia in patients with chronic pain. For example, Enarson, Hays, and Woodroffe (1999) demonstrated the efficacy of oral ketamine in patients who presented with chronic pain. Patients were initially given a divided dose of 100 mg per day, increasing the dose until efficacy was reached or the patients were no longer able to tolerate the psychoactive side effects. The analgesic benefits were most strongly observed in those with pain histories shorter than 5 years. Some patients did discontinue use due to psychotomimetic side effects, but most patients continued to successfully use ketamine at 100-240 mg per day for over a year (Enarson, Hays, & Woodroffe, 1999). In Russia as well, ketamine is at times prescribed as a painkiller for

those with serious illnesses (Jansen, 2004). This use of ketamine is especially interesting to mental health professionals because a relationship between high levels of depression and high levels of somatic pain has been observed (Banks & Kerns, 1996), so it would be of great value to find a medication that could effectively treat both problems.

OCD is an additional disorder with currently limited pharmacotherapy and psychotherapy treatment options. Recent research shows that the glutamatergic system may play a large role in the underlying biomechanism of OCD, and thus glutamatergic modulators, especially at NMDA receptor sites, may provide relief of symptoms. As of this writing, the safety and efficacy of a single dose of ketamine was being researched as a possible treatment for OCD at Mount Sinai Hospital in New York City, New York (Mount Sinai Hospital, 2014).

Ketamine is also presently being investigated for use in children. As of this writing, using intranasal Ketamine administration for treating bipolar disorder in children was being studied. According to the study's authors, the focus of the clinical trail was to investigate the safety and efficacy of ketamine administered intranasally to pediatric patients ages 6 to 12 years (Papolos, Teicher, Faedda, Murphy, & Mattis, 2013). Dr. Papolos is especially interested in ketamine's utility in helping children who suffer from profound fearfulness, aggression in response to perceived threats, and psychosis. This constellation of symptoms is called "fear of harm" (FOH) disorder and may be within the bipolar spectrum (Papolos et al., 2013).

Ketamine Versus ECT

ECT is a well-known and effective treatment for unipolar and bipolar depression (Ghasemi et al., 2013; Naughton et al., 2013). ECT is a treatment in which seizures are

electrically induced to produce relief from depressive symptoms. Despite its effectiveness compared to traditional antidepressants, ECT nonetheless requires a number of treatments to reach efficacy (Naughton et al., 2013). Research suggests that between five to seven treatments over the course of 3 weeks are necessary to significantly reduce depressive symptoms (Ghasemi et al., 2013; Naughton et al., 2013). Furthermore, ECT is also known for its memory-related negative side effects, including both retrograde and anterograde amnesia, as well as potentially adverse and lifelong cognitive effects (Benbow, 2004; Sackeim et al., 2007).

As ECT was previously thought to be the most rapid antidepressant treatment currently available, this indicates exciting potential for ketamine's use as an antidepressant as ketamine takes considerably less time—usually within 24 hr—than ECT to reach efficacy. For example, in research comparing the efficacy of ketamine and ECT for hospitalized patients with MDD, Ghasemi et al. (2013) conducted a blind and randomized study on a sample of 18 subjects in which half received three treatments of ECT and half received three infusions of 0.5 mg/kg of ketamine. The results showed that within 24 hr those who received ketamine demonstrated a significantly higher reduction in depressive symptoms as compared to the ECT group with a 50% to 90% response rate for the ketamine group (Ghasemi et al., 2013).

Additionally, ECT, since it requires a multiperson treatment team for administration and general anesthesia for the patient, is also a much more elaborate and expensive treatment to administer than ketamine. It should also be noted that ketamine's positive response for treatment-resistant patients also includes those resistant to ECT as first noted by Zarate et al. (2006) and confirmed by later studies.

Moreover, there is evidence that ECT and ketamine may work well when administered together. ECT has been demonstrated to be more effective when ketamine is used as the anesthetic agent. Ketamine has commonly been used as an anesthetic agent with ECT for decades, and two recent studies without control groups demonstrated that depressive symptoms decreased at a faster rate with ECT when the patients were given ketamine (Naughton et al., 2013). Some studies also suggest that when administered together, ketamine and ECT may produce synergistic antidepressant effects for patients with depression (Coppola & Mondola, 2012). Similarly, Okamoto et al. (2010) found that when ketamine is used as the anesthetic during ECT, the antidepressant response is achieved much more rapidly than ECT with a different anesthetic.

Psychedelic Psychotherapy

The premise of psychedelic psychotherapy is that the provider gives the patient an intoxicating, mind-altering, or vision-inducing substance in a controlled environment for a therapeutic purpose. This is not a new concept by any means. In the past, particularly in the 1950s to 1980s, the field of psychedelic psychotherapy was a widely explored avenue for therapeutic purposes, resulting in thousands of clinical trials and peer-reviewed research that assessed the safety and efficacy of such treatments (Goldsmith, 2007). However, unlike the notion today that views dissociative and psychedelic side effects as negative ones to be avoided or limited, the field of psychedelic psychotherapy embraced the hallucinogenic and mind-altering effects of psychedelic drugs as central to the therapeutic process. Psychedelic drugs, particularly LSD, psilocybin (hallucinogenic mushrooms), dimethyltryptamine (from the ayahuasca vine), and 3,4-methylenedioxy-N-methylamphetamine (MDMA; an amphetamine derivative), have been shown to be

helpful in the treatment of many psychological problems, including depression, anxiety, addiction, posttraumatic stress disorder (PTSD), grief and loss, and so on (Goldsmith, 2007). In addition, psychedelic drugs have been used in the past to aid in discovering the cause of a mental illness (i.e., as a diagnostic aid; Jansen, 2004).

During the time that psychedelic treatment was heavily researched, it was found that the safety of psychedelic drugs was generally high as they are nontoxic to adults, especially when compared with other drugs that are recreationally abused (Goldsmith, 2007). Nonetheless, it was found that psychedelic drugs are quite powerful and potent, and if used improperly or without adequate preparation they may result in psychological distress, which was usually brief (Goldsmith, 2007). Yet, when administered under the proper supervision, research showed that the use of psychedelic drugs in the context of therapeutic treatments demonstrated no long term deleterious effects (Goldsmith, 2007).

Practitioners and proponents of this therapy believed that these drugs can facilitate deeper exploration of the psyche as well as improve the efficacy of psychotherapy itself. Psychedelic psychotherapy has its roots in ancient shamanic and animistic traditions that stretch back thousands of years. Modern psychedelic psychotherapy began in the 1950s following the 1938 discovery of LSD by Albert Hoffman. Over the next 20 years, LSD and other drugs that produce psychedelic effects were researched in various clinical and outpatient settings (Dyck, 2005).

Over the course of investigating the potential benefits of these drugs, it was surmised that psychedelic drugs had the ability to tell us "more about how the mind constructs reality, personality, a sense of meaning and sacredness" (Jansen, 2004, p. 40). Timothy Leary, a well-known pioneer of psychedelic psychotherapy, strongly believed in

the drugs' positive attributes and their use as a form of therapy. Leary conducted research on a number of these drugs, including LSD and psilocybin; his studies included the famous Concord Prison Experiment (1961 to 1963) and the Marsh Chapel Experiment (1962, also known as "The Good Friday Experiment") in which he attempted to study the short-term and long-term effects of a mystical experience induced by psilocybin on various populations (Smith, 2002). Leary believed that a psychedelic experience provided patients with extraordinary psychological insight and interpersonal closeness, and, in the right environment, a therapeutic effect (Leary, 1969). When administered in supportive surroundings with adequate preparation, Leary found that psychedelic drugs allowed patients to gain deeper insights into their own actions and perspectives that were less self-centered, leading them to better understand their place in the world and their effects on others (Goldsmith, 2007; Smith, 2002).

In the 1970s and 1980s, Stanislav Grof was another leading voice on psychedelic psychotherapy. He noted that small doses of LSD had profound effects on the mental processes of study subjects, often producing euphoric experiences, and so he began to investigate LSD as a potential treatment for depressive disorders (Grof, 1980). The idea was that if LSD delivered what was essentially an emotional and/or cognitive shock, it may produce effects similar to ECT. Grof also used LSD in conjunction with conventional forms of psychotherapy based on his observation that LSD produced chemically induced activation, or an abreactive effect, making recipients more receptive to talk therapy. Over time, Grof became convinced that LSD-assisted psychotherapy was more effective for many patients than talk therapy alone (Grof, 1980).

Initially, Grof began with what he called a "psycholytic" approach, meaning the administration of mid-level doses of LSD (75 to 300 mg) on a recurring basis, the LSD was given at 1- to 2-week intervals, an LSD-assisted session lasted several hours, and all of the patient's thoughts and experiences were interpreted via conventional psychotherapeutic techniques (Grof, 1980). Later, Grof transitioned to the "psychedelic" approach, meaning the administration of a few high doses of LSD on an infrequent basis in an effort to induce mystical experience(s) (Grof, 1973, 1980). Early research on psychedelic psychotherapy, particularly with LSD, revealed the surprising result that the maximum therapeutic effects were achieved after highly positive and intense mystical or religious psychedelic experiences. The psychedelic treatment technique was conceived to better recreate these effects. Grof (1980) described the main objective of this type of treatment as inducing ego death and a transcendent state, one in which the subject experiences blurred boundaries of reality and euphoric sensations.

Over the course of his career, Grof conducted research on a wide variety of subjects, observing over 2,600 sessions with LSD, mescaline, psilocybin, and MDMA. He advocated that psychedelic drugs and the experiences they produced were not to be thought of as problematic side effects but rather as powerful and useful psychotherapy tools. According to Grof (1973), the psychedelic experience was one to be embraced as a legitimate technique for exploring the human unconscious. He compared the administration of psychedelic drugs as similar to other nondrug strategies used to explore consciousness such as meditation, hypnosis, sensory deprivation, and dream analysis (Grof, 1980).

Sadly, research on the potential usefulness of psychedelic medicines has all but come to a grinding halt due to the government's concern about the abuse of these materials and the increasingly restrictive regulations that virtually prohibit further study, despite the existing body of evidence that demonstrates the possible therapeutic uses for these medicines.

Summary

The research literature clearly demonstrated that low to moderate doses of ketamine produce remarkably rapid antidepressant effects in patients with MDD, bipolar disorder, and suicidality. Compared to other treatments for depression and bipolar disorder, ketamine is a novel option as it typically only takes several hours to reach efficacy as compared with selective serotonin reuptake inhibitors (SSRIs) that may take 3 to 6 weeks to produce the desired effects in patients. Ketamine has also been demonstrated to be significantly effective, showing reductions in depressive symptoms on a variety of measures in 70% to 90% of subjects in most experiments even though the subject groups were remarkably small in these early studies.

Ketamine also has a well-known safety profile, proven by its use over the past five decades as an anesthetic agent, and the early research showed similar safety levels when used for therapeutic purposes. Though intravenous administration of ketamine has been common, the literature supports that other routes of administration show promise, are well tolerated, and may make administration easier. Thus, ketamine's ability to be easily administered and to produce fast-acting antidepressant effects, particularly in patients who have not positively responded to other forms of treatments, indicates that it may be a pharmacological breakthrough in the field of depression treatment. Ketamine's

advantages over other currently available treatments mean that it could be administered in emergency and outpatient settings when rapid reduction of depressive symptoms to relieve a severe depressive episode or prevent self-harm is needed.

Previously, ECT was thought to be the only treatment that was faster acting than its pharmaceutical counterparts; however, it still took several weeks to reach efficacy and it is not without its risks and side effects. In contrast, by using ketamine for therapeutic purposes it may now be possible to induce rapid and robust relief from depressive symptoms in a single treatment, and the length of ketamine's effectiveness can probably be extended by multiple treatments. Ketamine can also be combined with ECT to produce a synergistic effect to increase the efficacy of both treatment approaches.

Research on the therapeutic uses of ketamine is still in its infancy, and many questions remain to be explored. Some of these issues will be explored in Chapter IV. Many of these questions pertain to determining which patients are the best candidates for ketamine treatment, using ketamine outside of controlled experimental settings, and grappling with the psychedelic component of ketamine treatment. Meanwhile, as researchers continue to think about the clinical applications of ketamine for depression, the research on ketamine is also shedding new light on the role of the glutamatergic system in the creation and treatment of depressive disorders.

CHAPTER III: METHODS

Overview of Methodology

The purpose of this study was to further psychologists' knowledge of ketamine as an adjunctive treatment for patients with depression and/or suicidal ideation. Ketamine is a medicine that is showing tremendous potential in treating depression, bipolar disorder, suicidality, and other psychological disorders. In this integrative literature review, what is known about the history of ketamine and its uses in anesthetic medicine was first summarized. Next, the small body of existing literature on experimental trials exploring ketamine's antidepressant effects was reviewed. Following this was a brief introduction to the field of psychedelic psychotherapy to help contextualize the use of psychedelic, egolytic, or dissociative medicines. It was believed that bringing this material together would aid in fluency and knowledge about ketamine while also set the stage to discuss some of the gaps in the research.

Objectives

The objectives of this study were to help psychologists learn more about ketamine as an option for treating depressive disorders and to suggest ways for them to participate in the growing research efforts on ketamine. To meet these objectives, psychologists need to know more about what ketamine is, how it works, existing research, and the strengths and weaknesses of this research.

Data Sources

The majority of the information for this study came from articles found in PsycINFO and PubMed. Search terms used included the following: ketamine AND (depression OR depressed), ketamine AND bipolar, ketamine AND (suicide OR suicidal),

ketamine AND side effects, ketamine AND ECT, ketamine AND (anesthesia OR anesthesiology), and psychedelic psychotherapy.

Supplemental material from several sources was also used, including online textbooks as reference materials for the sections on chemistry, anesthesia, and ECT. Information about the meningitis outbreak at Princeton, statistics on suicide rates, and information about current clinical trials also was found on the Internet. In addition to using published studies, I also drew from my personal collection of books for the section on psychedelic psychotherapy in Chapter II. Finally, information obtained through informal personal communications was included, both with other professionals (i.e., psychologists and psychiatrists) and patients, most of whom asked not to be identified in this study.

Analysis

I deconstructed existing material and generated original material in several places throughout this study. In Chapter II, I critiqued the methodologies used for several of the major clinical studies investigating the efficacy of ketamine as a rapid-acting antidepressant. The strengths and weaknesses of these experiments were integrated into the discussion of the published findings. Chapter IV, Results, enumerates the specific roles and responsibilities of the clinical psychologist regarding ketamine treatment with an emphasis on patient care. Chapter V, Discussion, focuses on how psychologists can contribute to the burgeoning field of research on the therapeutic uses of ketamine. Specifically, comments are made on several significant gaps in the existing body of literature, suggestions are made for future research, and comments on the clinical implications of current and future research efforts are provided. In addition, a frequently

asked questions (FAQ) sheet was created (see Appendix A) as a teaching tool for introducing psychologists to the topic of therapeutic ketamine. All analysis and discussion in the present study was qualitative.

Limitations

Two major limitations were encountered while conducting research for the present study. First, virtually all papers about ketamine were written by psychiatrists and were published in medical journals with medical professionals as the intended audience. Many articles assumed a certain familiarity with medical tests and terminology. This presented a significant barrier to access of information for nonmedical clinicians. Second, most of the information about psychedelic psychotherapy had to come from several decades ago due to governmental restrictions preventing research on the use of certain medicines, even ones that were shown to have significant therapeutic potential. These limitations made it difficult but not impossible for study objectives to be accomplished.

Delimitations

The decision was made to focus the research on articles that discussed the therapeutic uses of ketamine in human subjects who were also diagnosed with depression, bipolar disorder, and/or acute suicidal ideation. There was also a large body of literature on recreational ketamine use and/or substance abuse; articles with this focus were largely excluded from this study. Only articles that were available in English were considered; this did not appear to be a significant obstacle because all desired articles were available in English or there were translated versions available.

CHAPTER IV: RESULTS

The objective of this study was to help psychologists know more about ketamine as an adjunctive treatment for patients with depression and/or suicidal ideation. In Chapter II, I provided background information about ketamine and its uses in anesthetic medicine and other applications. I then summarized the recent findings about ketamine's antidepressant effects, including comments on the strengths and weaknesses of each experimental study. I followed this with a brief introduction to the field of psychedelic medicine, given that ketamine induces a temporary psychedelic state. The purpose of that material was to provide a strong basis for understanding where the field is regarding the use of ketamine as a treatment for depression. This material is summarized in an FAQ document that can be found in Appendix A.

Chapter Objective

The objective for this chapter is to discuss the role of the psychologist regarding ketamine treatment and patient care. Although ketamine is actually prescribed and administered by a physician (like all other antidepressant medications), psychotherapists must play an essential role in helping patients receive appropriate treatment and integrating this special type of treatment into their ongoing care. These responsibilities will be discussed in detail shortly.

One overarching theme of this chapter is thinking about ketamine treatment in a relational context that includes empathy for the patient's experience and time devoted to thoughtful reflection and meaning making. Sadly, many medical providers tend to focus on outcomes; it is essential for psychologists to be attentive to the entire process, including the decision to try therapeutic ketamine, preparing for the ketamine session,

assisting the ketamine experience, making sense of the ketamine experience, and so on. In other words, patients are likely to get the best outcomes when their treatment occurs within a collaborative partnership that is attentive to all of the patient's feelings, needs, and experiences. In many cases, patients have had the longest and most intimate relationship with their psychologist; therefore, the psychologist is a crucial member of the treatment team whose active participation must not be undervalued.

Role of the Psychologist in Ketamine Treatment

1. Identify which patients might benefit from ketamine treatment. Patients who are diagnosed with MDD and who experience periods of moderate or severe depression may be helped by ketamine, especially if they have been in talk therapy for a significant amount of time, have tried multiple medications, and still not have received adequate relief from their symptoms. Sometimes these patients are described as having treatment-resistant or refractory depression. Depressed patients who experience prominent suicidal ideation within the course of their depressive episodes may also benefit from ketamine. Patients with bipolar disorder who are currently taking a mood stabilizer or an antipsychotic medication (to minimize the chance of having a manic or a hypomanic episode) who are struggling with nonresponsive depression may also benefit from ketamine. (For more thoughts about different kinds of depression, please see Chapter V.) In addition, patients who are drug naïve (who have little experience with a substance-induced altered state) or patients who have a history of substantial addiction may not be good candidates for ketamine treatment. These considerations should be reviewed with the medical provider.

2. Discuss ketamine treatment as an option with the patient. Psychologists should be familiar with current research on ketamine for depression, the ketamine experience, the risks, the costs, and local resources for obtaining the treatment. Also, it is important to know that while ketamine is a legal medicine in the United States it is not yet FDA approved for treating depression. As such, this application is currently considered experimental. While it is legal for psychologists to discuss experimental treatment options with their patients, clinicians should consult with their own legal advisers if they have any concerns about recommending this type of treatment to their patients. A good guideline to keep in mind is that psychologists should know as much about therapeutic ketamine as they know about other antidepressant medications, and they should know when to make a referral to a psychiatrist or another medical professional. It is important not to practice outside of one's area of expertise and training. Ketamine treatment requires collaboration.
3. If the patient, psychologist, and medical provider all decide to go forward, the psychologist should help prepare the patient for the ketamine session in a variety of ways. It is important to explore the patient's hopes and fears about receiving a new and experimental type of treatment, including the possibility that it might not work the first time, it might not work at all, or might not work as well as the patient hopes it will work, and/or that the effects are likely to be temporary. In addition, many physicians tend to downplay or undervalue the psychedelic part of the ketamine experience; as such, patients can find themselves woefully unprepared for their session. In general, it is good to make sure that patients

understand they are likely to have a dissociative experience in which they may feel like a part of their awareness is temporarily leaving their bodies, and it is very important to tell them that anything that they may experience is temporary and that they will return to their premedicated state of consciousness in a short time (1 to 2 hr). It is a clinical judgment call about whether to tell patients more about what they might experience in their ketamine trip; some clients feel comforted by hearing or reading about other people's experiences while others prefer to let their experience unfold in an unprejudiced way. The psychologist can set the stage for future psychological work by telling patients that the images and mental experiences that occur during the ketamine session are meaningful and will be discussed in a postketamine psychotherapy session but that it is not necessary for patients to exert any effort to remember any part of their visions.

4. Do a formal or informal assessment of the patient's preketamine symptoms and level of functioning. Some specific areas to consider might include: cognitive clarity (does the patient feel like s/he can think), physical energy level, sense of self-worth, feelings of guilt, level of anxiety, suicidal ideation (the desire to die), problems with appetite, and/or problems with sleep. (Note that this list is not exhaustive.)
5. I highly recommend that the psychologist accompanies the patient to the ketamine session and sits with the patient during the treatment. There are several reasons for this. First, I have heard many stories (undocumented) of doctors or nurses giving an injection or setting up an IV of ketamine for a patient and then leaving the patient alone. To me, this is unconscionable. Even if there is another person

there, such as a nurse not known to the patient or even a psychiatrist that the patient only sees occasionally, it is not nearly as reassuring as having one's own psychologist there. Having a psychedelic experience that temporarily alters one's perspective and/or sense of self can be a fascinating but also a profoundly disorienting experience, and surely most people would take great comfort in the presence of someone with whom they have a deep and trusting relationship. Further, the psychologist can act as a note taker. Many patients who receive the currently recommended dose of ketamine (0.5 mg/kg) are capable of speaking a few words throughout their experience; they can tag important thoughts, images, and feelings that can be explored later in psychotherapy.

6. Work with the patient's psychedelic experience, treating it as interesting and meaningful. The imagery from the ketamine session can be approached in exactly the same way as dream material: Invite the patient to share whatever he or she remembers, ask for her or his associations to the imagery, ask about any feelings that were evoked at various times, and assist the patient in constructing meaning about her or his experience. It is important for the psychologist not to be fearful, dismissive, or enchanted with the material that was generated from the ketamine session solely because it was induced by a hallucinogenic chemical. It is important to remember that everything that the patient "saw" came out of the patient and is a part of her or his psyche.
7. Monitor the patient's progress over the days, weeks, and months following the ketamine treatment. The psychologist may want to repeat any formal or informal assessments of the patient's symptoms and level of functioning. This is important

for ascertaining whether or not the ketamine treatment was helpful for the patient, which specific symptoms were improved, how long the beneficial effects lasted, and so on. This information will be essential for planning future treatment as well as for contributing to the growing body of research about ketamine as a whole and specifically on its therapeutic uses.

8. Communicate with others about the efficacy of ketamine treatment. Which patients seemed most helped by it? Are there any thoughts or observations that may be of use to other clinicians or patients? It is important to share what one learns so that the suffering of others can ultimately be decreased. Publishing case studies would be of great value to the therapeutic community.
9. Advocate for the patient at any and every stage of the process. Patients who are severely depressed or suicidal may not be able to obtain the resources they need. The psychologist can act as liaison to other providers to help a patient have access to the kind(s) of adjunctive services such as medication management or ketamine treatment that might be called for in the patient's treatment plan.
10. Advocate for the community. Psychologists can look at the existing research about ketamine for depression and evaluate for themselves whether they think this is an area that is worthy of more research and funding. If so, they can speak with others, write letters, use social media, share information in conferences, and so on to raise awareness about this medicine and its potential usefulness. It is essential for psychologists to get involved in bringing this information to the attention of both the therapeutic community as well as the public at large. In the big picture, there is a social justice here: At present, the only patients who can currently get

experimental ketamine treatment are people who can afford to pay out of pocket for a private provider to administer it, usually costing hundreds of dollars. Psychologists need to take an active role in disseminating accurate information about ketamine treatment and fighting prejudice about it in the service of creating more affordable access to this treatment for everyone who needs it.

CHAPTER V: DISCUSSION

This chapter focuses on the role of the psychologist with respect to the burgeoning field of clinical research on the therapeutic uses of ketamine. Specifically, I will address some of the gaps in the existing body of research, and I will suggest some ideas for future studies to enhance the understanding of the appropriate uses and limitations of ketamine treatment. One key idea throughout this chapter is that it is essential for psychologists to actively participate in the research regarding ketamine. They can do this by critiquing the research that has already been conducted, collecting and analyzing data in current studies, and raising new questions to be investigated.

In the first part of this chapter, I consider some questions pertaining to the administration of therapeutic ketamine. While these types of decisions are mostly thought to be within the purview of medical professionals, I feel that the gaps in the existing literature are so significant that they need to be of concern to all clinicians. Further, it is only though discussion and collaboration with all members of a patient's treatment team that it is possible to arrive at answers to these questions. Therefore, these questions should be of interest to psychologists as well as psychiatrists and neurologists. In the second part of this chapter, I turn my attention to questions that pertain more directly to the scope and practice of clinical psychology. Finally, I end the chapter by discussing some future research directions that are being pursued.

Optimal Dose

A huge question that is begging to be asked has to do with the dose: Is more better? Specifically, does a bigger dose of ketamine produce a better (stronger) antidepressant effect or does the effect last longer? The currently recommended dose for

therapeutic applications of ketamine is 0.5 mg/kg, but it is also known that anesthetic patients routinely receive much higher amounts of ketamine to no ill effect. It seems that the next logical step in investigating ketamine for depression would be for a team to do an experimental study in which a group of depressed patients received 0.5 mg/kg of ketamine, 1.0 mg/kg of ketamine, and possibly 1.5 mg/kg of ketamine. The effect of these treatments on the patients' depression could be quantifiably measured using a variety of tools. A study of this kind could have three different groups of patients (an independent groups design), or every patient in the study could receive all three dosages (a repeated measures design), although in the latter case the researchers would have to take into account the possible cumulative effect of the ketamine treatments. In any event, it seems that the barrier to doing this type of study is the fear about creating a psychedelic experience that is too intense or dangerous for patients by giving them a higher dose of the medicine although there is no evidence whatsoever to support this concern.

Routes of Administration

How does ketamine's route of administration impact its effect? Is there any difference between receiving an IM injection and an IV infusion? I believe that an IV infusion gives a better outcome than IM injection because the provider can control the drip rate for an IV, slow down the rate at which the medication is administered, and thereby extend the length of time that the brain is exposed to the "chemical bath" that in turn may allow for more absorption of the medicine. A physician I know who administers therapeutic ketamine in his practice concurred with this idea (Physician A, personal communication, June 2012). In addition, IV ketamine has the added advantage of being a slightly more gentle experience, and patients are generally more able to be

verbal about their experience during their treatment. Further, IV treatment can be stopped at any time if the patient wishes whereas the patient is committed to the whole journey if he or she is given an injection. But, as previously noted, IV treatment requires more skill on the part of the provider and typically incurs more expense for the patient. In contrast, injections are quick and easy to administer. In thinking about IV administration, two ancillary questions arise: What is the optimal drip rate for IV treatment, and does the ketamine have to be pushed in at a particular rate in order for it to have a substantial antidepressant effect? I will return to a related question on this topic later in this chapter.

Another question about ketamine is whether other routes of administration (nasal, sublingual, oral, rectal, transdermal) work as well as IM or IV and whether these less invasive routes have any therapeutic applications? Anecdotally, I have heard many times that insufflating (snorting) dehydrated ketamine can give a user a "uplifting" effect that lasts several hours and possibly even into the next day, but it appears to impossible to get a profound antidepressant effect through insufflating ketamine crystals. Why would 200 mg of pure crystal ketamine taken through the nose be less potent than 50 mg of liquid ketamine injected into a vein? I have yet to find any physician or pharmacist who can explain this phenomenon to me. It appears that there is an upper limit to the amount of medicine that can be absorbed through the capillaries in the nose. Nonetheless, researchers are starting to experiment with low-dose ketamine (10 to 30 mg) compounded into a nasal spray for patients to use at home on a daily basis in order to extend the efficacy of the therapeutic ketamine session (Physician B, personal communication, April 2013). Similarly, I know a physician who is using low-dose ketamine in oral lozenges

with several severely depressed patients (Physician C, personal communication, May 2013). In both of these applications, the physicians report that the ketamine is subpsychedelic and has no noticeable cognitive or perceptual effects, but its efficacy has also not yet been established.

As previously discussed, oral ketamine (absorbed through the digestive tract) has poor bioavailability. Oral ketamine is known for being "body-heavy" and is mainly used for pain management. Clearly, oral ketamine will not produce as rapid an effect as IM or IV ketamine, but perhaps it will prove valuable for at-home use to extend the effect of a ketamine session.

Optimal Window for Treatment

So far ketamine has only been administered to patients who were quite severely depressed and/or suicidal as determined by clinical interviews and various inventories for depression. In general, therapeutic ketamine has been considered as "court of last resort" for treatment-resistant individuals in dire straights. The question of whether ketamine might be helpful for patients with a lesser degree of depression has not yet been addressed. There have been no studies to date that have looked at this question, and I believe this is likely due to a strong cultural bias against psychedelic medicine. However, prior to starting this study, I spoke informally with a number of patients who had received ketamine treatments for their depression (Patient A, Patient B, Patient C, personal communications, 2012-2013), and the consensus was that ketamine works better when it is administered sooner rather than later. In other words, when a patient with a chronic, recurrent mood disorder (either unipolar or bipolar depression) is heading into a depressive episode, ketamine treatment is more effective if the patient receives the

treatment before the depression becomes severe. This makes sense to me intuitively because, in a sense, there is less distance to travel to return the patient to a "normal" mood state. Perhaps it does not serve patients well to wait until they are in deep suffering to offer them ketamine treatment; this question clearly needs further exploration and study.

Multiple Treatments

For some patients, one ketamine treatment is not enough to get a substantial antidepressant effect or the antidepressant effect only lasts a few days. As previously noted, several researchers have started to investigate multiple ketamine infusions or serial treatments clustered close together to create a cumulative effect. It is never known how many treatments individual patients might need to lift them out of a severe depression; some patients appear to get great benefit from a single ketamine treatment while others get a better result with two, three or even six treatments (Krystal et al., 2013). It is essential that providers talk with patients about the possibility that they will need more than one treatment so their expectations are realistic.

The timing of multiple (serial) treatments is another area that research has not yet adequately addressed. The few existing clinical experiments (Cusin, 2012; Murrough, 2010) spaced the ketamine treatments at 2 to 3 days apart. However, it is also known that some patients experience an antidepressant effect that lasts anywhere from 3 to 14 days from a single ketamine treatment. To my knowledge, no study has been done that has looked at readministering ketamine after a longer interval. This is clearly a gap in the research that needs to be addressed.

Using Ketamine Over Time

The research on the antidepressant effects of ketamine is still in its infancy. A significant question that has not yet been addressed is if ketamine can be used repeatedly over significant periods of time in the long-term management of a patient's depressive disorder. This question can be broken down into several component issues. First, there is the question of efficacy. Will ketamine work as well the third time or the tenth time as it does the first time? As previously noted, it is known from self-reports of heavy recreational users of ketamine that people can become habituated to ketamine's effects over time and require more and more of the material to achieve the same hallucinogenic effect. However, at this point it is not known with how many exposures to ketamine and at what dose levels habituation becomes a concern, so this is an area that requires further research.

Next, there is the question of safety. Although ketamine is used extensively in anesthetic medicine and has an excellent safety profile in that application, it is necessary to still proceed with caution when thinking about administering ketamine repeatedly over time. Since there is no experimental data on this from humans, animal models must be looked to for information. In studies on long-term ketamine use in animals (rats and monkeys), it has been demonstrated that daily ketamine administration produced glutamatergic synaptic deficits that resulted in the animals showing an amotivational state, negatively affected cognitive function, and reduced ligand binding to frontal cortex NMDA receptors (Krystal et al., 2013). While no one is suggesting that any human patient receives a therapeutic dose of ketamine on a daily basis, nonetheless it is

important to be mindful of the potential risks of using a psychoactive medicine that disrupts a signaling pathway of a major neurotransmitter.

In addition, there is the very important question of psychological safety. Would repeated ketamine exposures increase a patient's risk for having a psychotic break? This is obviously an extremely difficult question to investigate experimentally because of the ethical issues involved. But in order to even contemplate this question, it must be asked what exactly is the relationship between having a psychedelic experience and "becoming psychotic?" Does one necessarily precipitate the other? In order to even begin to answer this question, it is necessary to look at the understandings and associations to the words themselves. Psychedelic is derived from the Greek words meaning to make the soul visible (Merriam-Webster.com, 2014) and connotes an expansion of consciousness. In contrast, the synonyms for psychotic include "crazy, deranged, mad, demented" (Merriam-Webster.com, 2014). The connotations of a psychotic experience suggest something that is overwhelming, frightening and/or chaotic, and also something that is profoundly unpleasant. By paying close attention to the language used, it can clearly be seen that a psychedelic experience and a psychotic experience are not the same the thing; these terms should not be used interchangeably and there is no clear relationship between them.

From there, it can be asked how ketamine is similar to and different from other psychedelic medicines. Is there a way to prepare the patient and the setting so as to minimize the risk of an adverse outcome? Is there any evidence to suggest that the risk of psychosis increases with repeated administrations of ketamine, or does the risk of psychosis actually decrease as a patient becomes more comfortable with and able to

navigate the psychedelic space of the ketamine journey (which is what is suggested by every shamanic tradition from every culture around the world)? All of these questions need further exploration.

In addition, I have never seen anyone anywhere even pose the question of a possible rebound effect. Is it possible that having a ketamine treatment and getting temporary relief from depressive symptoms could cause a worsening of depression as the medication's effects wear off? To my knowledge, no one has considered this possibility. To provide a possible starting point for thinking about this issue, I am extrapolating from what I know about MDMA, which also has a profound but short-lived antidepressant effect, granted via a different neurochemical pathway than ketamine (Parrott, 2001), and from the repeated use of benzodiazepines, which also work via a different chemical pathway than ketamine (Herman, Brotman, & Rosenbaum, 1987). Both chemicals provide a desirable psychological effect in the short term but after repeated uses they both can lead to a rebound effect or a worsening of symptoms as the medications wear off. While neither of these examples are particularly relevant to ketamine because their chemistry is so different, as noted they nonetheless provide a starting point for thinking about this issue. As the research on therapeutic ketamine moves forward, I think this is yet another question that should be considered.

Concerns About Addiction

Another question that must be addressed is whether therapeutic ketamine treatment, either a single session or many sessions over time, puts a patient at risk for ketamine abuse or addiction. In other words, does medicinal use lead to nonmedicinal use, which is a pattern of use that is commonly seen with prescription opioid medications.

There is no evidence from the literature on surgical anesthesia to support this concern. However, more research in this area is needed. Specifically, longitudinal studies are needed that follow ketamine patients for a period of years following their ketamine treatment(s) to look at changes in their recreational drug usage. This is where psychologists can be especially useful in gathering and sharing this important information from their long-term patients.

Interactions With Other Medications

As ketamine use is considered for more patients, another question that comes up is whether it is safe and effective to combine ketamine treatment with other medication regimens. In virtually all of the experimental studies to date, the subjects were required to discontinue their regular medication regimen for at least 2 weeks prior to receiving the experimental ketamine treatment. Obviously, this approach is not realistic or desirable for a real world application, especially in the event that a patient receives multiple ketamine treatments clustered together and/or receives repeated treatments over time. What needs to be ascertained is whether there is any danger to the patient if ketamine is combined with particular medications, such as monoamine oxidase inhibitors (which are used rarely in psychiatry nowadays but are sometimes still used when patients demonstrate severely refractory depression), or if the efficacy of the ketamine treatment is comprised if patients are taking a medication such as an benzodiazepine as a part of their regimen. Also, what effect does an antipsychotic medication have on ketamine treatment? Atypical antipsychotics (i.e., Aripiprazole) are frequently used as an adjunctive pharmacotherapy for treating depression. Also, what about interaction effects with medications that patients might be taking for other, nonmental health reasons?

While the field of anesthesia has provided some information on this, much more is needed in order to use ketamine safely in an outpatient setting.

Different Kinds of Depression

In the experimental studies that looked at using ketamine to treat subjects with major depression, the subjects were described as having long histories of chronic, recurrent depressive episodes. Based on my observations over the past few years, it appears that ketamine treatment works best for people with depression who also have a significant family history of depression or mental illness and who experience a significant somatic component to their depressive episodes in the form of loss of energy, difficulty moving (psychomotor retardation), difficulty with speech production, loss of appetite, and/or changes in sleep patterns. For me, this raises the question of which patients are likely to benefit from ketamine treatment, and are there patients who are not likely to benefit from it. In other words, there are many different causes and presentations of depression—will they all respond equally well to ketamine? The early experimental data suggests that patients with organic MDDs with a strong hereditary component may respond well to ketamine treatment although the studies to date have included a small number of subjects. But what about people without a history of depression who become severely depressed or suicidal following a traumatic event (where the primary diagnosis is PTSD) or the loss of a loved one (where the primary diagnosis is bereavement)? What about patients who can best be described as having a depressive or masochistic coping style (concepts that are taken from psychoanalytic theory) and who have profound feelings of emptiness or self-hateful thoughts but who lack the somatic features of MDD? Could ketamine be useful for any of these patients?

Further, again returning to the broad category of MDD, it is important to keep in mind that there is tremendous variation in people's individual experience and presentation of this disorder. Researchers and clinicians needs to ask if there are certain profiles or features that are associated with more successful or less successful treatment outcomes with respect to ketamine. For example, I know several physicians who have been reluctant to give ketamine to severely depressed patients who also present with prominent anxiety (Physician D, personal communication, June 2012; Physician E, personal communication, April 2013). The rationale for this is that ketamine has both sedating and stimulating properties, and there was the concern that the ketamine treatment might induce additional anxiety. However, I recently spoke with a patient diagnosed with depression and anxiety who received ketamine treatment and who reported that the ketamine eliminated her anxiety for nearly a week following the treatment (Patient A, personal communication, March 2013). While this one example may or may not point to a generalizable clinical phenomenon, it does open the door for the question to be asked: Do we need to reexamine the inclusion and exclusion criteria for ketamine treatment?

Along these same lines, depressed patients with a history of psychosis were excluded from the studies on ketamine for depression. At some point in the future, it will be important to carefully explore the question of whether it is truly dangerous to induce a dissociative, transpersonal, and/or psychedelic experience in a patient who has experienced some form of psychosis in the past, especially since the patients with schizophrenia in Krystal's original research (1998) reported that they found ketamine to be beneficial. This question also seems to me to be of particular significance when

thinking about providing treatment to patients with bipolar disorder (type I). Given that many bipolar patients experience some sort of distortion in their relationship with external, consensual reality during the course of their manic episodes, it is especially hard to know where to draw the line for "too much psychosis" when working with this population. As the clinical research on therapeutic ketamine continues, it is possible that the findings will help to illuminate the biological mechanisms that underlie different kinds of depressive disorders and also point the way toward additional treatment options.

Also, I want to point out that there is often a tendency in the psychological and the psychiatric literature to refer to depression as a singular phenomenon, as though it is something that could even be cured or mitigated by an injection. This way of thinking grossly oversimplifies and underestimates the devastating effects of a chronic illness like severe MDD or bipolar illness that not only impacts, among other things, a person's cognitions and self-perception but also his or her social/relational functioning and capacity to work and induces anger in itself (as opposed to being caused by it). It has yet to be seen how ketamine treatment will truly help the subgroup of patients who are dealing with severe and debilitating chronic conditions. It is important that clinicians do not lose sight of the comprehensive biopsychosocial interventions that are needed to help these patients have the fullest, least-encumbered lives possible.

Suicidal Patients

For the purposes of this discussion, it is useful to consider that most suicidal patients fit into one of three broad categories: patients whose suffering has become unbearable, patients who repeatedly become overwhelmed and use suicidal thinking as an internal or interpersonal coping strategy, and patients who are treated by emergency

responders and whose history is unknown. The early data show that ketamine treatment significantly but temporarily reduces suicidal ideation (the desire to end one's life) in patients with long histories of severe depressive illnesses and in a small naturalistic study. There have been no experimental studies to date on using ketamine with patients where the primary diagnosis was history of trauma or relational difficulty (i.e., a personality disorder). So it is not known whether ketamine would be helpful in decreasing suicidal ideation for patients who fit this description.

As previously noted, suicidal patients who treated by in emergency rooms and hospitals pose a special challenge for providers because their physical and mental health history is typically not known. It is a clinical judgment call as to whether an individual patient might benefit from ketamine treatment. It should be noted that patients who find themselves in a hospital situation are usually desperate and frightened. This is not a good mindset for entering into a disorienting psychedelic experience so great care must be taken to adequately prepare the patient for the treatment if it is the chosen course of action. The advantage of ketamine treatment is that is has the potential to be effective in short order. I predict that as the body of research on ketamine grows, guidelines will be published regarding the administration of ketamine in psychiatric emergency departments.

The Psychedelic Experience and the Antidepressant Effect

The medical model for understanding ketamine treatment says that the ketamine molecule does something on a strictly biochemical level that changes the way the brain works to relieve the symptoms of depression. According to this model, the psychedelic effects of ketamine are an annoying and undesirable side effect that needs to be minimized. I have come to believe that this model is incomplete. I think a new paradigm

needs to be embraced stating that ketamine acts both on chemical and psychospiritual levels. The evidence for this way of thinking about ketamine comes out of users' self-reported experiences of feeling deeply loved, interconnected, and communing with divinity (Jansen, 2004; Sewell, 2007). This type of information about the ketamine experience is missing from the formal, peer-reviewed, and medical research literature because many researchers do not value the psychedelic experience enough to pay close attention to it. However, if a true understanding of what ketamine does and how it works is to be gained, I assert that it will be necessary to pay close attention to *all* aspects of the ketamine experience, including the parts that seem outside the realm of typical, contemporary clinical practice.

I have noticed that there appears to be a correlation between how psychedelic a ketamine session is perceived to be and how powerful the antidepressant effect is perceived to be and that this is independent of the actual dose although this idea has not been supported by the experimental studies done to date. Nonetheless, this observation has led me to wonder about the relationship between the psychedelic experience and the antidepressant effect. Perhaps having a psychedelic experience; that is, a change in perspective or having access to a new kind of emotional or spiritual realm, is essential to the antidepressant action of this material. I believe that this question could be tested using a fairly simple experimental design. Here is the concept: It is a well-established fact that barbiturates, benzodiazepines, and opioids tend to reduce the hallucinogenic properties of ketamine (Enarson et al., 1999; Stevenson, 2005). Ketamine is often administered in combination with one or more of these medications during surgical anesthesia for a variety of reasons. For the purpose of this discussion, these medicines

will be called "mitigators." I propose an experiment in which a group of subjects with severe depression receive therapeutic ketamine treatment alone at the currently recommended dose (0.5 mg/kg), and another group of subjects receives therapeutic ketamine plus one of the mitigators. The presence of the mitigator should reduce the intensity of the psychedelic experience. The purpose of the study would be examine the relationship between the intensity of the psychedelic experience, which can be rated using existing measures, versus the antidepressant effect. My hypothesis is that a less intense psychedelic experience would be correlated with a less profound antidepressant effect.

If my hypothesis is correct, it would completely change the way the medical community and the pharmaceutical industry think about ketamine. Currently, most providers are preoccupied with minimizing the psychedelic effects of the treatment, and many drug companies are searching for a ketamine analogue that works without inducing a psychotomimetic state.

The Ketamine Experience

As previously noted, it is essential for researchers to start paying more attention to what exactly is happening for patients during their ketamine experiences and reporting this in the literature. This information will help other clinicians prepare their clients for ketamine treatment, it may yield some clues as to how ketamine works, and it may provide further ideas for other ways to treat depression. There is abundant material about people's experiences that can be found on the Internet or that is noted anecdotally in books about recreational drug experimentation, but none of this information has been collected in a systematic way that can be verified.

Of particular importance is publishing accounts of patient's negative experiences with ketamine treatment, if they occur. There are two kinds of "negative" experiences: those that are difficult in the moment but that get worked through and result in an acceptable (or desirable) outcome and those that lead to serious negative consequences. As previously noted, one of the greatest fears about therapeutic ketamine (and all psychedelic medicines) is that it might cause some patients to have psychotic breaks. It is essential for psychologists to publish longitudinal case studies that either confirm or refute this concern.

Another interesting question is how quickly ketamine produces an antidepressant effect. Two hr is the minimum time frame that is commonly seen in the most recent literature. However, I think that this is incorrect: it is based on the fact that it generally takes about 2 hr postinjection for a patient to have recovered enough to complete the required posttreatment measures. But as researchers begin to pay closer attention to what is actually happening during the ketamine treatment, I think they will find that some patients actually begin to get some relief from their depression about 20 min postinjection, that it is possible for patients to indicate this in some way, that the antidepressant effect continues to grow or take hold over the next several hours or days (Physician A, personal communication, August 2013), and that further research will validate this finding.

Further, there appears to be a window of opportunity to do some deep therapeutic work with most patients just after the mental effects of the ketamine treatment begin to recede but the medicine has not been fully metabolized by the body and the patient still feels somewhat physically sedated and uncoordinated (Physician A, personal communication, March 2014). The exact timing of this occurrence varies from person to

person based on the dose of ketamine received, the route of administration, and the individual's metabolism, but often occurs around the 45-min mark for patients who received 50 mg of ketamine IM and lasts for at least 30 min. This is a time when many patients want to share what they have just experienced and appreciate the presence of a supportive guide who can provide reassurance and a reminder of the patients' values, goals, and coping strategies. It is striking that there is no mention whatsoever in any of the psychiatric literature about this phenomenon or the need for a psychospiritual intervention at this juncture.

Ketamine-Assisted Psychotherapy Revisited

If serious consideration is given to the possibility that ketamine facilitates a psychospiritual experience, then it must again be asked if it has any usefulness as a tool for personal growth and self-exploration. In other words, the possibility must be considered that ketamine could be used as a tool in psychotherapy, not just for patients with severe or refractory depressive illnesses but also for a broader range of clients. I realize that this is a highly sensitive and controversial issue; nonetheless, I think the question merits consideration, especially as the profession moves forward in trying to understand how ketamine works and what exactly it is doing. It is exactly at this point that neuroscientific research on the mechanisms of ketamine converges with the data from clinical research and the history of psychedelic psychotherapy to create a new field of inquiry about the nature, safety, and efficacy of nonordinary states of consciousness.

Patient History and Cultural Context

One general criticism that could be made about the existing experimental literature on therapeutic ketamine is the lack of published information and/or discussion

about the demographics of the subjects. While it is obviously important to protect the privacy of the participants, this information is also needed in order to establish the external validity and generalizability of the findings. For example, while most of the major studies published the ages and genders of the subjects, many did not indicate the subjects' race/ethnicity, sexual orientation, marital status, or religious affiliation. It is unknown whether any of these variables would prove to be significant with respect to ketamine's therapeutic efficacy. However, it would be interesting to take a closer look at some of these variables. For example, it might be interesting to study whether individuals who grew up in a religious tradition that normalized or embraced mystical experience or divine communion had a subjectively different experience of the psychedelic component of ketamine treatment as compared with patients who did not grow up in those kinds of traditions. In other words, to what degree does one's comfort level with mystical experience influence his or her dissociative experience during treatment? Further, therapeutic ketamine is currently being studied in many countries including the United States, Britain, Korea, Italy, Spain, Germany, and Brazil. Would cross-cultural studies show any differences in patient's attitudes towards ketamine treatment or the ketamine experience, perhaps as a reflection of dominant social values? Psychologists must never lose sight of the larger social context in which dysfunction and treatment occurs and which defines what is considered normative.

Current and Proposed Clinical Trials

There are a myriad of current and proposed clinical trials on ketamine's use as a rapid antidepressant. In March 2014, a search on www.clinicaltrials.gov, a registry and database of clinical studies from around the world using human participants as the

subjects, for ketamine and various mental health conditions yielded over 100 results. Some of the areas that seem to be receiving the most resources and attention at this time include the following:

- Replicating the antidepressant effects of ketamine in larger studies.
- Doing further studies on the use of ketamine with patients who are experiencing suicidal ideation.
- Extending the antidepressant effect of ketamine by either doing a series of ketamine treatments or by administering an additional medication.
- Mitigating the psychedelic component of ketamine treatment by using other agents/medications that block ketamine's psychotomimetic effects.
- Using ketamine and ECT together.
- Investigating ketamine treatment in previously excluded populations, notably in patients who meet the criteria for both major depression and alcohol use disorder, children diagnosed with bipolar disorder, and depressed adolescents.
- Researching the efficacy of ketamine in the treatment of other mental disorders including OCD, PTSD, and social anxiety.

It is also interesting to note what topics are not being addressed by current research efforts, namely whether ketamine is useful to patients who are experiencing moderate depression, patients who have some active psychotic symptomology, and patients whose depression is thought to be in response to trauma (as opposed to hereditary/congenital); and depression in the senior population. In addition, there are no currently posted studies that appear to be an inquiry into the ketamine experience itself,

perhaps using low-dose administrations that would allow participants to be more communicative about their journeys.

Related Chemicals

In addition to ongoing research on ketamine's efficacy as a therapeutic treatment, several other NMDA antagonists are currently being investigated to ascertain whether they are capable of producing similar antidepressant effects. One such chemical is GLYX-13, referred to as a molecular cousin to ketamine, which may be able to produce some antidepressant results without creating psychedelic effect. GLYX-13 is a bigger molecule than ketamine and it does not appear to block the receptor ion channel as ketamine does, which is speculated to be the reason that it does not produce hallucinogenic effects in users (Moskal et al., 2005). Recently, a Phase 2 clinical trial was conducted in which GLYX-13 was administered to small group of patients with treatment-resistant depression. Significant reductions in depressive symptoms were recorded, appearing within 24 hr of treatment and lasting for approximately one week. The drug was well tolerated and no hallucinogenic side effects were noted (NIMH, 2013). This drug is scheduled for further testing during 2014 to see if the findings hold up.

Methoxetamine (MXE) is another interesting molecule. MXE was reportedly first synthesized several years ago by chemists who were looking to get around the legal prohibition against ketamine in some countries (Craig & Loeffler, 2013). It is chemically very similar to ketamine but was engineered to be more potent. It also appears to have a greater affinity for the NMDA receptor site than ketamine, causing it to "stick better" in that receptor and have a longer-lasting effect. Whereas 100 mg of insufflated ketamine induces a 1- to 2-hr altered state in users, the same amount of insufflated MXE induces a

4- to 6-hr altered state (Patient B, personal communication, December 2013). While there is no doubt that MXE is highly hallucinogenic, there are conflicting reports as to whether MXE has potent antidepressant properties. A small study done in 2012 by Coppola and Mondola demonstrated that MXE produced rapid antidepressant effects in patients who had both treatment-resistant and nonresistant depression, but there is an abundance of unverified, personal reports on the Internet indicating that MXE has little or no antidepressant effect (Erowid, 2014). Clearly this is an area that needs further study.

CHAPTER VI: CONCLUSION

In this study, the goal was to introduce readers to the topic of therapeutic ketamine as a novel and rapid-acting intervention for the treatment of severe depression, bipolar disorder, and suicidality. Although ketamine is a pharmaceutical intervention that has to be administered by a medical health professional, the emphasis was on the role of the psychologist with respect to ketamine treatment.

Taken together, the major findings from the experimental research to date are that ketamine can produce a robust but temporary antidepressant effect in as many as 80% of subjects with severe, treatment-resistant depression. The antidepressant effect can occur in as little as 2 hr after treatment and typically lasts between 3 and 14 days. As it stands now, ketamine fills a critical gap in the treatment of depression as it is the only rapid-acting intervention that is available. In contrast, it often takes 3 to 6 weeks for a traditional SSRI medication to reach its full effect. However, because of its controversial psychedelic component, ketamine is has only been studied in patients with severe depression or suicidality. It is currently considered a last resort option when all other options have been exhausted. It is not known whether ketamine can or should be used on an ongoing basis for the management of chronic depressive disorder.

Chapter IV, Results, focused on the role of the psychologist in patient care with respect to therapeutic ketamine. Specifically, I enumerated 10 specific roles and responsibilities of the clinical psychologist as part of the treatment team providing care to a depressed, bipolar, or suicidal patient who might benefit from ketamine treatment. These jobs include identifying which patients might need ketamine, helping patients access the resources they need, preparing patients for the treatment, sitting with patients

during treatment, doing pre- and posttreatment assessments, helping patients make sense of the psychedelic component of their experience, and monitoring patients' moods over time. In addition, I discussed the FAQ sheet created to introduce psychologists to basic information about ketamine for depression. This document can be found in Appendix A.

In Chapter V, Discussion, the objective was to demonstrate how psychologists can and need to participate in the research efforts to learn more about therapeutic ketamine. I elucidated some of the gaps in the existing body of literature and suggested several experiments that might help the research community to better understand the risks and benefits of this treatment. One major point that I made in this chapter is suggesting a new paradigm for thinking about ketamine. Instead of thinking about it acting on a purely chemical level, I proposed that it be conceptualized as acting simultaneously on both physical and psychospiritual levels. In this new paradigm, the psychedelic visions induced by ketamine are no longer viewed as a problematic side effect but rather understood to be part of the healing action of the material and integral to the antidepressant effect. Only further observation, research, and open-minded discussion will reveal whether this new paradigm has any value, but I think it is worthy of consideration.

Going forward, several things are becoming clear. First, it appears that neuroscience is on the cusp of a new era with the respect to understanding and treating depressive disorders. The discovery of ketamine's antidepressant effects and other NMDA antagonists has given researchers an important clue into the possible role of glutamate in mental dysfunction. I predict that ketamine will be the new Prozac in the sense that it will likely be followed by a number of other, related medicines made by

different manufacturers that all work in a similar way. Second, for the time being it is becoming increasingly clear that clinicians will need to become more comfortable and more competent in working with nonordinary states of consciousness in order to help their patients benefit from ketamine and its derivatives. While this area is usually thought to be the domain of anesthesiologists and psychedelic shamans (neither of whom are trained the diagnosis and treatment of mental illnesses), the time has come for mental health professionals, including psychologists, to examine their own prejudices in order to make the best use of all currently available treatment options. Preparing patients for a nonordinary experience and helping them make sense of that experience is absolutely the psychologist's responsibility. Providing state-of-the-art treatment to alleviate mental suffering, helping patients cultivate a sense of curiosity about the thoughts and images generated by their minds, and accepting their experiences without judgment is at the heart of our work as psychologists.

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APPENDIX A

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FAQs About Ketamine for Depression

What is Ketamine?

Ketamine is medication that is primarily used in surgical anesthesia. It is categorized as a dissociative anesthetic. It was first discovered in the 1960s and has been used successfully all over the world to perform millions of surgeries in the past 50 years. Recently, ketamine has also been found to have a profound antidepressant effect as well. The use of ketamine to treat psychiatric disorders is controversial because ketamine is a highly hallucinogenic substance, briefly inducing a psychedelic, depersonalized, or altered state of consciousness.

Who Might Benefit From Ketamine Treatment?

Patients with severe depression (major depressive disorder with recurrent depressive episodes), bipolar patients with severe depression, depressed patients with suicidal ideation.

How Long Does it Take to Achieve an Antidepressant Effect?

The antidepressant effect may be noticeable in as little as 2 hours after injection, or it may take several days for the antidepressant effect to reach its full effect.

How Long Does the Antidepressant Effect Last?

This varies from person to person. The antidepressant effect often lasts for approximately two weeks from a single injection, but may last for as little as 3 days, or in some cases, the beneficial effect may last for several months. The latest research shows that the antidepressant effect of ketamine can be extended by administering a series or a cluster of treatments together.

How is Ketamine Administered?

Therapeutic ketamine is typically administered by intramuscular (IM) injection. This can be done by a medical health professional on an outpatient basis. It can also be administered as an intravenous (IV) infusion.

What does a Ketamine Treatment Feel Like? What Does the Patient Experience?

While medicated with ketamine, many patients describe the experience of having their spirit or their essence temporarily leave their bodies. In some cases, patients feel as though they are hovering above the treatment room; in other cases, they feel as though they are hovering above the earth. Themes frequently reported by patients about their visions include love, connectedness, and/or divinity. The vast majority (over 90%) of patients in the clinical experiments to date described their psychedelic experiences on ketamine as "pleasant."

How Long Does a Ketamine Treatment Take?

The dissociative, psychedelic effect of ketamine generally lasts about 60 minutes. A sedated or heavy feeling in the body can persist for an additional 60 minutes. Most ketamine sessions are scheduled for 4 hours.

Is Ketamine Treatment Safe?

Yes, ketamine has a well-established safety profile from its use in anesthetic medicine. It is considered one of the safest anesthetics known.

What Are Ketamine's Side Effects?

Ketamine's side effects are usually mild and transient. They can include nausea, headache, muscle aches or spasms, and hypertension (increase in blood pressure). In the past, disorientation, psychosis, and alterations in sense of self were also listed as possible side effects of anesthetic ketamine. These are not considered side effects with respect to therapeutic ketamine treatment as changes in perspective and/or alterations in sense of self may be essential to the antidepressant effect. The one serious side effect that has been linked with prolonged ketamine use is cystitis or damage to the bladder. This problem has only been seen in recreational users who have taken ketamine hundreds of times (or more) and has never been seen in a patient who received ketamine in a medical setting. Nonetheless, it is a concern for patients who might need ketamine on a repeated basis.

Is Ketamine Addictive?

Addiction is not a concern for patients receiving medically supervised ketamine.

How does Ketamine Work?

The primary action of ketamine is as an allosteric (indirect) blocker of the N-methyl-D-aspartate (NMDA) receptor sites in the brain and central nervous system. In doing so, ketamine temporarily interferes with the transmission of glutamate, an excitatory neurotransmitter. In addition, ketamine appears to bind to a variety of other receptors throughout the brain and may promote the formation of new neural connections. However, the exact mechanism(s) for how ketamine reduces depression and/or suicidal ideation are not fully understood at this time.

What Does the Experimental Research Say About Ketamine's Effectiveness for Treating Depression?

Ketamine has been studied in small, carefully controlled experiments using control groups and/or double-blind protocols. These experiments have shown that ketamine can significantly reduce the symptoms of depression or suicidal ideation on a

temporary basis for the majority (up to 80%) of the individuals to whom the drug was administered.

Is Ketamine Legal?

Yes, ketamine is a legal medication that can be prescribed by any physician with a DEA number. It is FDA approved for use in anesthesia and analgesia (pain management). Using ketamine to treat depression is currently considered experimental and it is not yet FDA approved for this purpose. The FDA is already scheduled to review the literature on ketamine for depression in 2017. Note that ketamine is a Schedule III substance, meaning that it is a controlled substance.

What is the Role of Psychologists With Respect to Ketamine Treatment?

It is essential for psychologists to be knowledgeable about ketamine for two reasons: to improve patient care and to contribute to research efforts. Regarding patient care, psychologists need to be able to identify which of their patients might benefit from ketamine treatment (assessment), prepare a patient for ketamine treatment, and to know how to sit with a patient during ketamine treatment. They also need to know how to help a patient make use of the material that was generated in the ketamine session (integration), and they need to follow the patient's progress. Regarding contributing to the research efforts, psychologists can critique the existing literature, suggest new research questions, and function as members of research teams.

How Do I Find a Medical Professional to Administer Ketamine to My Patient?

Check with the psychiatry department at your nearest university or hospital. More and more physicians in private practice are beginning to offer ketamine treatment as well.

How does Ketamine Compare With ECT for Treating Depression?

Ketamine has many advantages over ECT: It is easier to administer than ECT, it is far less expensive than ECT, it does not cause cognitive impairment or memory loss, and it can work within a few hours of the first treatment. However, the beneficial effect of ketamine does not last as long as a full course of ECT; they serve different purposes in

this regard. Research also indicates that ECT may work better when ketamine is used as the anesthetic for the procedure. Ketamine and ECT are complementary treatments; they are not mutually exclusive.

Will Ketamine Replace Other Kinds of Treatment for Depression?

No. Ketamine is meant as an adjunctive treatment to be used in addition to psychotherapy and pharmacotherapy. For now, it is used when other treatment options have been exhausted or when the patient's condition worsens.

Are There Other Uses for Ketamine?

Yes, ketamine is currently being studied for use in patients with obsessive-compulsive disorder, alcohol addiction, opioid addiction, seizure disorder, complex regional pain syndrome, and in children who have "fear of harm" disorder.

What Else Do I Need to Know? Where Can I Find More Information About Ketamine?

The information about the therapeutic uses of ketamine is changing rapidly. The ethical psychologist will stay informed on the latest developments. At present, PubMed is a great source of information although the information is becoming more widely available as more people become aware of the importance of glutamatergic medicines in treating depression.