

● INVITED REVIEW

Practical application of the neuroregenerative properties of ketamine: real world treatment experience

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Abstract

While controversial, ketamine has emerged as an effective treatment for refractory depression. Serial infusions have been performed 3 times per week, but our practical experience has challenged this precept concerning infusion frequency. Depression is associated with neuron loss, reduced synapse numbers, and dearborization of dendrites. Ketamine appears to potently induce mechanisms which reverse these neurodegenerative processes. Ketamine not only blocks the glutamate receptor, it activates eukaryotic elongation factor 2 (eEF2). This, in turn, activates brain-derived neurotrophic factor (BDNF) protein synthesis. This is thought to underlie ketamine's enduring benefits. In addition, ketamine alters glycogen synthase kinase-3 (GSK-3) phosphorylation, probably responsible for its rapid antidepressant effect. Notably, inhibition of the BDNF receptor does not block the immediate benefits of ketamine, but does prevent the enduring effects. Neuro-Luminance Ketamine Infusion Centers have been treating patients with serial ketamine infusions for over three years. Our methods differ from what is often reported, as we perform infusions only once per week and generally do not perform more than five infusions. Data from 100 patients showed that 80% of the patients responded. The baseline Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score was 17.8 ± 2.8 . Responders to ketamine showed a drop in QIDS-SR score of 10.8 ± 3.5 , while non-responders showed a 0.8 ± 1.8 change. Moreover, they often had persistent benefits over several months. Recently, it was proposed that psychotomimetic effects are necessary during a ketamine infusion to yield effective antidepressant benefits. Yet, only one patient in our clinic has experienced hallucinations in three years. Nevertheless, 80% of our patients show clinical improvement. Further studies of clinical methods for ketamine infusion therapy are encouraged.

Key Words: Ketamine; brain-derived neurotrophic factor; infusion therapy; depression; safety

"It is now widely accepted that ketamine is an effective and fast-acting antidepressant, proven to be beneficial for a variety of depressed patients" - Scheuing et al. (2015) National Institute of Mental Health.

"The fleeting nature of ketamine's therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution" - Newport et al. (2015) American Psychiatric Association.

Introduction

While controversial in academic settings, ketamine has emerged as a highly effective treatment in refractory depression. Multiple centers now exist in several countries to aid those with treatment-resistant depression. I am the medical director of one such center. The wealth of clinical experience from treating hundreds of patients with ketamine has supplanted the preliminary data that emerged from the initial open-label and small double-blinded studies. Herein, I will briefly review the published clinical studies of ketamine infusion for depression from the perspective of dosing protocols, explore the purported mechanisms of ketamine as an antidepressant, and outline my own clinical experience in terms of dosing based on the neurobiological mechanisms of ketamine. My endeavor is to illustrate three points: 1)

dosing based on the neurobiological mechanisms is likely to be more beneficial and cost effective, 2) the antidepressant benefit of ketamine is not dependent upon having a hallucinatory experience, and 3) enduring antidepressant effects can be achieved with ketamine and reflect its purported neuroregenerative properties.

What is Ketamine?

Ketamine is a dissociative anesthetic in use since 1970 (Jansen, 2000). Ketamine has poor bioavailability by oral route (30%) and low bioavailability by intranasal route (30–50%). It is metabolized by N-demethylation to norketamine (Aroni et al., 2009), then to 5-hydroxynorketamine and eventually to dehydronorketamine (the most prevalent metabolite in the urine). It increases blood pressure in some, but does not

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suppress respiratory drive. Anesthetic doses typically range from 1–4.5 mg/kg (Barash et al., 2013; package insert). The common side effects at anesthetic doses are elevated pulse and blood pressure, somnolence, confusion, dream-like states, vivid imagery, hallucinations, diplopia, nystagmus, nausea, and vomiting. Ketamine also is used as a street drug. Abuse doses range from 1 to 40 mg/kg (Jansen, 2000; Wood et al., 2011; Tam et al., 2014; package insert). A user-oriented website provides insight into the expected side effects in this doses (thegooddrugsguide.com). The doses for the treatment of depression vary from 0.5–1.0 mg/kg (see below). The most common side effects in doses used for depression treatment include: dizziness, nausea, and a slight sense of dissociation. The side effects clear generally within 15–30 minutes after the infusion.

A Novel Antidepressant?

The seminal study by Berman and colleagues (2000) showed that sub-anesthetic dose infusions of ketamine produced a rapid antidepressant response. Additional studies of single infusions of ketamine confirmed this initial finding – ketamine at 0.5 mg/kg infused over a 30–40 minute period induces a rapid reduction in depressive symptoms and suicidal ideation in approximately 60–75% of patients (Berman et al., 2000; Zarate et al., 2006; Price et al., 2009). This stood in marked contrast to the disappointing performance of oral antidepressants, which require weeks to work and rarely achieve better than a 40% response rate (Connolly and Thase, 2011; Newport et al., 2015). One limitation of ketamine was the symptom relief typically lasted only 4–10 days. Multiple infusions were explored, but how often should infusions be given? The decision was made to give infusions 3 times per week. This was not based on an understanding of the unique pharmacology of ketamine, but merely because this was the treatment protocol of electroconvulsive therapy or ECT (P.R. Shiroma, personal communication). As a result of this almost random decision, the “established” protocol for ketamine became 3 times per week; however, is this frequency supported by the mechanisms of action of ketamine?

Possible Mechanisms of Depression

Depression is associated with a loss of neurons, reduced synapse numbers, and dearborization of dendrites in the hippocampus and frontal cortices (Cook and Wellman, 2004; Lui et al., 2008; Duman, 2014; Morais et al., 2014). In essence, depression is a model of reversible neurodegeneration. Currently available monoaminergic antidepressants can potentially increase neural progenitor cells in the hippocampus of rodent models (Duman, 2014) and humans (Boldrini et al., 2009), as well as upregulate brain-derived neurotrophic factor (BDNF) (Engel et al., 2013). Methods of preventing neurogenesis, such as focal irradiation (Surget et al., 2008) or focal knockdown of the BDNF expression can prevent the behavioral response to monoaminergic antidepressants. Similarly, dendritic arbors are denuded in animal models of stress (Cook and Wellman, 2004; Liu et al., 2008) and dendritic spine density markedly decreases (Liu et al.,

2008; Duman and Duman, 2015). These structural rearrangements can be partially reversed with monoaminergic antidepressants (Morais et al., 2014; McAvoy et al., 2015). These changes are manifested grossly since the size of the hippocampus is reduced in patients with depression (Sheline et al., 1996) based on MRI. Hippocampal volume briefly enlarges following ECT treatment for depression (Nordanskog et al., 2014) and possibly following transcranial magnetic stimulation treatment for depression (Furtado et al., 2013). Monoaminergic antidepressants do not induce hippocampal enlargement (Godlewska et al., 2014).

Possible Mechanisms of Action of Ketamine

The mechanisms underlying the antidepressant effects of ketamine are not simply due to glutamate receptor inhibition. Rather, ketamine binding to an N-methyl-D-aspartate receptor (NMDAR), if coupled to a mature α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, activates eukaryotic elongation factor 2 (eEF2) *via* a kinase. This, in turn, activates BDNF protein synthesis, particularly in neuronal dendrites (Browne and Lucki, 2013; Monteggia et al., 2013; Bjorkholm and Monteggia, 2015). The concomitant depolarization of AMPA receptors leads to calcium-dependent exocytosis of BDNF, which can then bind to post-synaptic tyrosine receptor kinase B (trkB) receptors (Browne and Lucki, 2013; Scheuing et al., 2015). TrkB receptors initiate numerous pathways, including early response genes and the mammalian target of rapamycin (mTOR) pathway which also leads to increased BDNF translation (Duman, 2014; Scheuing et al., 2015). Moreover, BDNF has the ability to regulate mTOR and, thus, creates a positive feedback loop leading to further increase of BDNF production (Hoeffler and Klann, 2010). Of note, higher anesthetic doses of ketamine do not activate mTOR in an animal model, suggesting a therapeutic window for ketamine (Li et al., 2010). mTOR is localized in the dendrites and can rapidly initiate the translation of synaptic proteins and other mediators of neuroplasticity. Post-mortem studies of patients with depression have revealed decreased BDNF expression in the hippocampus (Chen et al., 2001; Dwivedi et al., 2003) and loss of neurons. Knockdown of BDNF levels in the hippocampus manifest depressive behaviors in mice (Taliaz et al., 2010). Rodent models of stress-induced depression also show decreased BDNF expression in the hippocampus, which can be reversed with ketamine (Browne and Lucki, 2013), over-expression of trkB (Koponen et al., 2004), or local micro-infusion of BDNF (Shirayama et al., 2002; Gardier, 2013). Other NMDAR antagonists, such as memantine, lack the antidepressant effects of ketamine and this difference appears to reflect ketamine’s distinct ability to inhibit the phosphorylation of eEF2 and upregulate the expression of BDNF (Gideons et al., 2014; Bjorkholm and Monteggia, 2015).

Glycogen synthase kinase-3 (GSK-3), which is believed to function abnormally in mood disorders, also appears to be altered by ketamine (Zunszain et al., 2013). Increased phosphorylation of GSK-3 induced by ketamine is a possible mechanism for its rapid antidepressant effect. For example,

a knock-in mouse model, wherein GSK-3 cannot be phosphorylated, lacks an antidepressant response to ketamine (Beurel et al., 2011). GSK-3 is thought to induce mTOR activity which could lead to increased BDNF levels (Duman, 2014). The well-known antidepressant and mood stabilizer, lithium, which also inhibits GSK-3, potentiates the effects of ketamine on GSK-3 and lithium pretreatment has been proposed as a method of prolonging the antidepressant benefits of ketamine (Zunszain et al., 2013; Scheuing et al., 2015).

The inhibition of the ketamine's antidepressant effects has been explored by many laboratories. Blocking the AMPA receptor appears to prevent the effects of ketamine on animal models of depression (Zunszain et al., 2013). Blockade of mTOR with rapamycin pretreatment also prevents the antidepressant effects of ketamine in animal models (Li et al., 2010). Notably, trkB inhibition does not block the immediate benefits of ketamine, but does prevent the enduring effects (Browne and Lucki, 2013). These studies have been extensively reviewed elsewhere (Monteggia et al., 2013; Zunszain et al., 2013; Scheuing et al., 2015). A tyrosine kinase inhibitor, which prevents the autophosphorylation of trkB, blocks the sustained antidepressant effect of ketamine (as measured at one week in an animal model), but only if administered prior to the ketamine (Carreno et al., 2015). Furthermore, this sustained antidepressant response could be prevented by administering lidocaine to the ventral hippocampus immediately prior to administering ketamine systemically (Carreno et al., 2015). Notably, neither transient silencing of neuronal impulse activity in the ventral hippocampus nor inhibiting auto-phosphorylation of the trkB receptor prevents the immediate antidepressant benefit of ketamine in this animal model, but either eliminated the sustained effect.

Curiously, ketamine also appears to have immunomodulatory effects and these may prove important mediators of its persisting benefit. Ketamine is believed to suppress a transcription factor important in the expression of inflammatory mediators, such as interleukin-6 and tumor necrosis factor alpha (Miller et al., 2009; Duman, 2014). It can rapidly decrease levels of pro-inflammatory cytokines in the hippocampus (Wang et al., 2015). Notably, these cytokines can alter numerous monoaminergic pathways, as well as suppress BDNF production (Felger et al., 2013). Ketamine also may alter the kynurenine pathway (Zunszain et al., 2013), which may mediate several mediators of inflammation in the brain.

Taken together, these data posit that ketamine has both immediate and delayed effects. The immediate effects include: presynaptic disinhibition of glutamatergic neurons, creating a glutamate surge; increased activation of the AMPA receptor in conjunction with inhibition of NMDAR; inhibition of GSK-3; and synaptogenesis and synaptic potentiation resulting from translation of BDNF and activation of the mTOR pathway. The delayed effects of ketamine likely include: activation of eEF2 leading to BDNF translation; enhanced synaptic connectivity; neurogenesis; dendritic arborization; and immunomodulation. Neuronal activity (as well as trkB auto-phosphorylation) in the ventral hippocampus is required for the delayed effects of ketamine

to occur. The delayed effects potentially underlie persistent neuroplasticity and persistent antidepressant effects. These mechanisms may also underlie the neuroregenerative properties of near-infrared light, which also activates BDNF and has immunomodulatory effects (Morries et al., 2015).

Practical Application of Molecular Mechanisms

The Neuro-Luminance Ketamine Infusion Centers have been treating patients with serial ketamine intravenous infusions for over 3 years. Patients are given infusions using infusion pumps, administered by certified registered nurse anesthetists (CRNA), supervised directly by a psychiatrist, and with extensive monitoring of ECG, blood pressure, pulse oxymetry, and end-tidal carbon dioxide levels. A crash cart, oxygen, and defibrillator are present. Side effects were limited to elevated blood pressure in a small number of cases, nausea in a modest number of cases, and dizziness in most cases. None of the patients endorse hallucinations or dysphoria. All patients were monitored for at least 30 minutes after each infusion.

In our clinic, we have not followed the capricious protocol of Shiroma and colleagues (2014) for multiple infusions. Rather, we have given infusions of ketamine no more than once per week. Our patients receive a mean of 4.3 infusions in total and 80% have clinical improvement based on standardized depression scales. The timing of the infusions is not lock-stepped. Each patient's infusion schedule is individually determined based on his/her response. Some patients will receive three infusions in 3 weeks, while others will receive three infusions spread out over 7 weeks. The result is clinical improvement with much fewer infusions for most patients. From a mechanistic standpoint, this can only be possible if ketamine is inducing increased BDNF which leads to lasting changes in synapses, dendrites, and neuronal circuits.

A portion of our patients consented to use of their data and we have analyzed the first 100 such cases. Just over 51% were female, 99% were Caucasian and the mean age was 41.2 ± 14.5 years. Eighty percent had recurrent unipolar depression, while the remainder had recurrent bipolar depression. All had failed at least 5 antidepressant medications. Nineteen had failed to respond to ECT or transcranial magnetic stimulation. The baseline Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score was 17.8 ± 2.8 , which places them in the category of severe depression (cutoff 16). Twenty percent did not respond to ketamine infusion therapy using our protocols. Responders to ketamine showed a change in QIDS-SR score of 10.8 ± 3.5 , while non-responders showed a 0.8 ± 1.8 change (Figure 1). For many, this represented a decrease from severe depression to the range of symptom-free to mild depression. We have followed up with our patients over 2–30 months and most remain on oral medications, but with controlled symptoms. For them, this represents a tremendous clinical improvement.

Suicidal ideation was a prevalent symptom at baseline among our patients. Virtually every patient endorsed thoughts of suicide. Seventy-two percent scored a 2 or 3 on

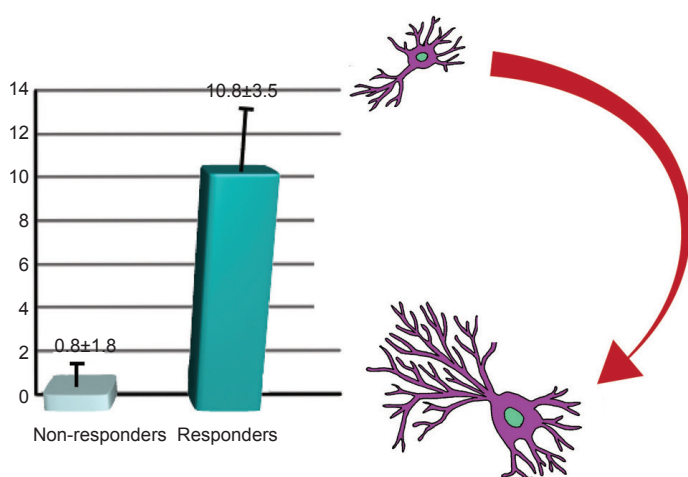


Figure 1 Changes in depression scale score.

Change in Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score was 10.8 ± 3.5 among the 80% of patients who responded to ketamine infusions, while non-responders showed a 0.8 ± 1.8 change. Weekly or even less frequent ketamine infusions appeared to yield effective long-term antidepressant benefits. Activation of brain-derived neurotrophic factor (BDNF) appears to have an important role in the antidepressant effects of ketamine. BDNF induces synaptogenesis, dendritic arborization, improved neuronal health, and neurogenesis. These processes likely underlie the persistent benefits of ketamine.

the QIDS-SR Question #12 (either “I think of suicide or death several times a week for several minutes” or “I think of suicide or death several times a day in some detail or I have made specific plans for suicide...”). Notably, suicidal ideation was decreased in most patients, including non-responders, often after the first infusion. This is consistent with the observations of Murrough and colleagues (Murrough et al., 2015).

Additional Observations

We have also explored the possibility in approximately ten patients that lithium pre-treatment may potentiate or prolong the antidepressant benefits of ketamine based on lithium’s ability to potentiate the inhibition of GSK-3 (Scheuing et al., 2015). To date, adding oral lithium in the days prior to a ketamine infusion has yielded no notable difference in patient response. Similarly, lithium pretreatment also has not converted ketamine non-responders into responders in our clinic. Our analysis of all non-responders has not yielded any clear distinguishing factor(s). An unknown factor among our non-responders may be the presence of the Val66Met single nucleotide polymorphism of the BDNF gene which has been shown to reduce responsiveness to ketamine in animal models (Browne and Lucki, 2013; Duman, 2014).

Two other observations, which have not been systematically evaluated, but are pertinent to issues of debate concerning the most effective use of ketamine, are offered. Patients who have tried intranasal ketamine from other providers within Colorado have reported no or transient benefit. Approximately 50% of those who tried intranasal ketamine experienced bladder pain and cases of ulcerative cystitis were encountered among those who had tried intranasal ketamine prior to coming to our infusion clinic for care. We have avoided the use of intranasal ketamine due to the risk of ulcerative cystitis and other urological complications (Wood et al., 2011; Tam et al. 2014). The second observation relates to the use of cannabis and/or benzodiazepines concomitantly with ketamine infusion therapy. Among our patients, 29% were using benzodiazepines as part of their daily routine and 19% were using cannabis

daily or almost daily. There was no difference between responders and non-responders on this attribute. Moreover, we have often pretreated patients with 1 mg midazolam intravenously and have not found this to interfere with the likelihood of antidepressant response.

The Psychotomimetic Theory

Recently, the theory has been advanced that psychotomimetic effects are necessary during a ketamine infusion to yield effective antidepressant benefits (Sos et al., 2013). This theory has become somewhat popularized and was discussed at length at the recent Kriya Institute conference on the use of ketamine (November 7–8, 2015, San Mateo, CA, USA). While hallucinations are a potential side effect of ketamine, only one patient in our clinic has experienced hallucinations in three years. Yet, 80% of our patients show clinical improvement. The index study by Sos and colleagues (2013) used the equivalent of 0.72 mg/kg over 40 minutes, which is 44% higher than the standard dose in our clinic. Similar doses were discussed among those attempting to generate hallucinatory experiences during depression therapy. Doses in the range of 0.7–1.0 mg/kg over 40 minutes are likely to increase psychotomimetic and other adverse effects, but based on our experience do not enhance the antidepressant benefits. This may assuage the somewhat alarmist views expressed in dogmatic opinion pieces in the absence of actual clinical experience with ketamine (Lieberman, 2015).

Abuse Potential

Given the concerns raised by Newport and colleagues (2015) and Lieberman (2015) that ketamine could be addictive and ketamine infusion centers could be potentially responsible for setting off a firestorm of ketamine abuse/addiction in the United States, it seems ironic that none of our patients have pursued getting “extra” infusions. Indeed, multiple patients have approached us about getting a refund on the unused portion of a treatment package, citing that they had no need for additional ketamine. Now, while the multiple of “anecdote” is not “data”, our clinical experience is that patients undergoing our protocols do not become addicted

to ketamine and the “slippery slope” from treating depression to creating a ketamine addiction is not so precipitous as Newport and colleagues (2015) in absence of real-world experience and in the presence of significant commercial affiliations (see disclosures – Newport et al., 2015), would lead us to believe.

Neurotoxicity

Similarly, reports of white matter lesions and neuronal injury attributed to ketamine have only been identified in ketamine abusers (Liao et al., 2010; Edward Roberts et al., 2014), who are using 3–10 times (see the drug abuse advice website thegooddrugsguide.com for dose ranges) the dose used in the treatment of depression (as well as using multiple drugs of abuse). Animal studies suggesting daily dosing of ketamine can lead to neurotoxic effects were using 3 mg/kg – roughly 6 times the dose used in our clinic (Featherstone et al., 2014). This is not unlike the pathological effects of methylphenidate, which is widely used at 1 mg/kg to treat attention-deficit-hyperactivity disorder (ADHD). At very high doses (5 mg/kg), it can cause cardiomyocyte lesions (Henderson and Fischer, 1995), but at therapeutic doses there are only rare instances of such pathology (Fischer and Barner 1977; Ny-mark et al., 2008).

Summary

Since a major mechanism by which ketamine relieves depression is by the activation of multiple pathways leading to the enhanced expression of BDNF, it is possible that long-lasting alterations in the neurons, dendrites, spines, and circuits may occur with repeated ketamine infusions. The Neuro-Lumiance Ketamine Infusion Centers have been treating patients with serial ketamine infusions for over 3 years. Our methods differ from what is often reported; as we perform infusions only once per week and do not often perform more than five infusions in most cases. Data from 100 patients showed that 80% of the patients responded. Moreover, they often had persistent benefits over several months. Further controlled studies of the best clinical methods for ketamine infusion therapy are encouraged.

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