



3-1-2020

## In Patients with Treatment-Resistant Depression, How Effective is Ketamine for Rapid Improvement of Depression and its Symptoms?

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### Recommended Citation

Ghohestani-Bojd, Sara, "In Patients with Treatment-Resistant Depression, How Effective is Ketamine for Rapid Improvement of Depression and its Symptoms?" (2020). *Physician's Assistant Program Capstones*. 58.

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**In Patients with Treatment-Resistant Depression, How Effective is Ketamine for Rapid Improvement of Depression and its Symptoms?**

By

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Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfilment of the requirements

for the degree of

**MASTER OF PHYSICIAN ASSISTANT STUDIES**

March, 2020

## Introduction

Mental health is one of the most significant, and often overlooked, aspects of the healthcare system. The consequences of a neglected psyche can trigger substantial damage to the physical body over time. Unlike preceding generations, today's society has become inundated with constant technological advancements and an unhealthy obsession with productivity. This situation can contribute to a lack of meaningful social connections, impossible to reach societal standards, a lack of a work-life balance, and perhaps most importantly, an overwhelming emotional burden.<sup>1</sup> Unfortunately, this emotional burden is often perceived as an impediment in a productivity driven world, rather than as a precursor to harmful mental and physical health outcomes. It is no wonder, then, that clinical research in medicine continues to uncover connections between a lack of emotional wellbeing and the risks of developing chronic diseases. Evidence now exists demonstrating the means by which persistent stress and anxiety can essentially cause damage to the brain by altering neural pathways. Over time, this brain damage can lead to neuropsychiatric disorders such as chronic depression, bipolar disorder, PTSD, and dementia.

Major depressive disorder (MDD), also known as unipolar depression, is a serious chronic mood disorder that has a lifetime prevalence of 16.6% in the US. According to the World Health Organization it is the leading cause of disability.<sup>2</sup> It can cause severe symptoms that affect one's emotions, thoughts, social life, physical health, sleep habits, eating habits, ability to partake in routine daily activities of living, and even the will to live. Although numerous well-established treatments for MDD are available (e.g., anti-depressants, psychotherapy, somatic interventions, electroconvulsive therapy (ECT), transcranial magnetic

stimulation (TMS), et cetera), a large population of patients do not respond to these conventional treatments. One of the largest and most comprehensive clinical studies on MDD, Sequenced Treatment Alternative to Relieve Depression, demonstrated that improvement of depressive symptoms is only achieved in about 30% of patients after the first antidepressant medication

### Depression treatment by the numbers

Of the roughly **17 million** adults in the US who struggle with depression...



around **11 million** receive some kind of treatment — therapy or medication.



Of this 11 million people who receive treatment, around **50 percent** experience at least a temporary reduction in symptoms.



Only **30 percent** of patients receiving treatment for depression reach full recovery or remission.



Roughly **30 percent** of people with Major Depressive Disorder (MDD) remain depressed despite trying multiple, structurally distinct antidepressants. These "treatment resistant" patients have been studied in most clinical trials of ketamine.



About **60 percent** of treatment-resistant MDD patients are likely to respond to ketamine, preliminary evidence suggests.



SOURCE: REPORTING BY E. UNDERWOOD

KNOWABLE MAGAZINE

trial.<sup>3</sup> Moreover, the odds of improvement lessen with subsequent antidepressant medication trials. Clinically, patients who fail at least two trials of antidepressant drugs from different pharmacologic classes are categorized as having treatment-resistant depression (TRD). The

foregoing findings have vast implications for the wellbeing of patients experiencing treatment failures.

Chronic suicidal ideation (SI), a common symptom of TRD, puts these patients at greater risk of engaging in suicidal behaviors.<sup>4</sup> Suicide is a psychiatric emergency, for which there are no currently approved rapid onset medical treatments. The standard available pharmacological antidepressants can take weeks to months to achieve desired effects. As a result, the estimated 400,000 individuals per year who seek emergency treatment for suicidal thoughts and behavior often do not get timely relief.<sup>5</sup> According to the CDC, suicide is the 10<sup>th</sup>

leading cause of death in the US and it takes the lives of approximately 45,000 Americans every year.<sup>5</sup>

For decades clinicians and scientists have been searching for an alternative to rapidly treat patients with TRD. This dilemma may be partly resolved for some patients. A new use for an old drug, ketamine, promises to be effective for treatment of TRD. This new role for ketamine will be explored with particular emphasis on whether it is effective, and if so, how durable its benefits are.

### **Historical Context**

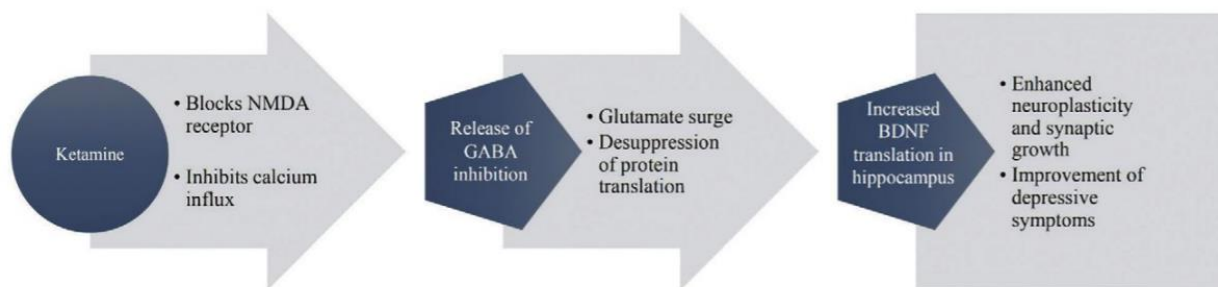
Prior to the discovery of ketamine, phencyclidine (PCP) was one of the main anesthetics used. It not only caused the adverse effect of delirium, but also became a drug of abuse. These disadvantages prompted the search for a better agent. In 1962 chemists discovered ketamine, a structural analog of phencyclidine with one-tenth the potency of PCP.<sup>6</sup> Within two years the first human trials with ketamine began to explore its potential applications.<sup>6</sup> In 1970 the FDA approved ketamine for use in anesthesia. Historically, ketamine has been a popular anesthetic because it produces analgesia/sedation, amnesia, and lacks significant respiratory depression. Given ketamine's ability to preserve cardiorespiratory stability within a large therapeutic window, anesthesiologists and critical care specialists regard it as an invaluable resource for anesthesia and sedation. However, during the late 1970s, after gaining popularity in the medical field, ketamine became more readily available and subsequently became a source of problems. Due to its effects of disassociation, ketamine was used and sold recreationally leading to problems with drug abuse and addiction.<sup>6</sup> As a result, ketamine eventually fell out of favor as a first line anesthetic/sedative agent and is now considered a schedule III-controlled substance.

For decades afterwards many medical providers have feared exploring the possibilities of ketamine's use outside of anesthesia. Despite its negative reputation, some clinicians still maintained a healthy curiosity in its potential. Beginning in the mid-1990s at Yale University, researchers started exploring ketamine's use in depression.<sup>6</sup> Over the last two decades and counting, data from a growing number of clinical trials have been compiled into dozens of review papers, meta-analysis, and retrospective studies. The evidence from these data suggest that in small doses, ketamine can produce a rapid, effective treatment for patients with TRD. Interestingly, in March of 2019, the FDA approved intra-nasal esketamine (Spravato™) (a doubly potent chemical cousin to ketamine) to be used in conjunction with an oral antidepressant for treatment resistant MDD.<sup>7</sup> It is not known whether its side effect profile, dosage, route of administration and antidepressant actions are superior, equal to, or inferior to those of ketamine. Thus, more research was necessary to characterize treatment of depression with ketamine and esketamine. Recent investigations are helping to better understand their roles.

### **Background/Science**

The field of psychiatry is enthusiastic about the findings that ketamine has rapid-onset antidepressant effects in patients with TRD. However, the exact mechanism of this therapeutic effect remains a topic of debate. Ketamine's primary known mechanism of action involves blocking the N-methyl-D-aspartate receptor (NMDAR), a glutamate receptor found in nerve cells of the brain.<sup>8</sup> Glutamate is the predominant neurotransmitter in the brain and is involved in every major excitatory brain function. Its role is to facilitate communication cross networks of cells in order to execute complex central nervous system (CNS) functions such as hearing, vision, and movement.<sup>8</sup> Ketamine blocks this sensory input which accounts for most of its

known effects in anesthesia. However, it is unknown if this blockade of NMDAR is the primary contributor to ketamine's antidepressant effects.



**Figure 1. Potential MOA of Ketamine in Treating Treatment-Resistant Depression (intext cite)** Abbreviations: BDNF, brain derived neurotrophic factor; GABA,  $\lambda$ -aminobutyric acid; NMDA, N-methyl-D-aspartate.

A second contributing mechanism of action (MOA) that might explain ketamine's antidepressant effects was theorized in 2017 by Ionescu and Papakostas.<sup>9</sup> Ketamine increases expression of brain-derived neurotrophic factor (BDNF), a protein that promotes the survival of neurons in the CNS.<sup>9</sup> This elevation in BDNF in the hippocampus is thought to promote neuron and synaptic repair which likely contributes to ketamine's rapid antidepressant-like effects.<sup>6</sup> In other words ketamine permits neuroplasticity, which is crucial given depression's known association with prolonged neurodegeneration.<sup>9</sup>

A final important mechanism of action of ketamine is its reduction of inflammatory cytokines<sup>10</sup>, which have been linked to mood disorders. Interestingly, ketamine is the only anesthetic drug to have a strict inhibitory effect on pro-inflammatory cytokine signals.<sup>10</sup> Clearly, ketamine has multiple mechanisms of action which work simultaneously, making it a unique drug in comparison to traditional antidepressant medications. Traditional medications mostly attempt to increase the level of neurotransmitters such as norepinephrine, dopamine and serotonin. The delay in effectiveness of these antidepressants has suggested that medication-

induced changes in neurotransmitters are still several steps away targeting the root cause of depression. In contrast to other non-pharmacological forms of depression therapy, ketamine is widely available and its use does not require providers trained and equipped to use specialized devices such as with ECT and TMS.<sup>11</sup> Needless to say, it is an exciting time for the field of psychiatry to explore the possibilities of ketamine's rapid improvement of symptoms in TRD.

### **Discussion of Findings**

By the late 1990s there was a growing body of preclinical research implicated that ketamine's NMDA receptor antagonist behavior may have antidepressant activity. The psychiatric community was eager to start trialing. In 2000, the first clinical trial reporting the antidepressant effects of ketamine was conducted by R.M Berman et al. and published by Biological Psychiatry Journal.<sup>12</sup> This randomized, double-blinded study tested seven subjects with major depression over a period of 2 days. Participants received either a saline solution (placebo) or ketamine (control) administered intravenously at 0.5 mg/kg over a period of 40 minutes in this study. They were evaluated at baseline and post infusion at 80 minutes, 230 minutes, 24 hours, 48 hours and 72 hours after starting infusion. The Hamilton Depression Rating Scale (HDRS) was used to evaluate mood changes pre and post infusion. The results of this study showed low dose IV infusions of ketamine significantly reduce HDRS scores compared to saline (placebo). Patients reported a diminution of depressive symptoms within 3 days post infusion. Ketamine's rapid onset of action in contrast to that of traditional antidepressants generated considerable excitement.

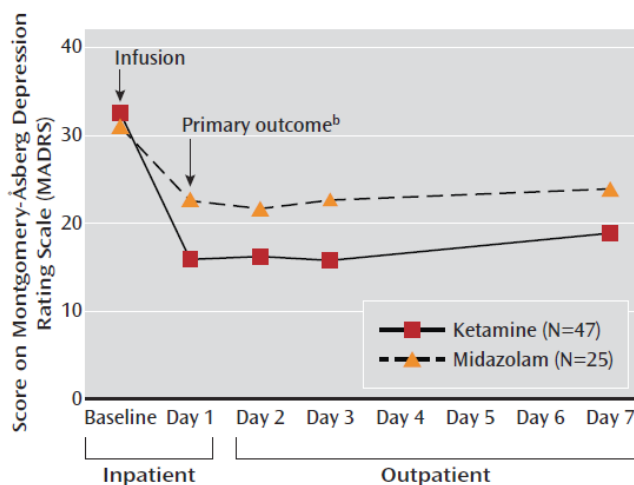
In 2006, with the support of the National Institute of Mental Health, Zarate et al. designed another randomized, placebo-controlled, double-blind crossover study to determine the effects of



IV infusions of ketamine vs placebo on TRD over the period of a year.<sup>13</sup> This study was higher in budget, had eighteen subjects and lasted much longer than the previous study. Results showed that subjects receiving ketamine showed 71% of the subjects had a significant improvement in depression within 110 minutes after injection. The remission response remained significant for up to a week in 35% of the subjects. This study was important for the trajectory of ketamine as a viable option for TRD because it points to a potential for longer lasting effects. Still, some skeptics regarded the antidepressant effects of ketamine to be a result of its psychoactive nature (mind-altering effects) rather than a true pathological improvement of neurological pathways leading to depression.

In a 2013 study by Murrough et al., for the first time, ketamine was compared with a *psychoactive* placebo, midazolam.<sup>14</sup> This was a two-site, parallel arm, randomized controlled trial of a single infusion of ketamine compared to an infusion of midazolam. Using the Montgomery-Asberg Depression Rating Scale (MADRS), the researchers assessed outcomes and found that the ketamine group had a greater improvement in the MADRS score than the midazolam group 24 hours after treatment. A response rate of 64% improvement for symptoms

FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam<sup>a</sup>



From Murrough et al (2013) Am. J Psychiatry

of depression was found for the patients who received ketamine as compared with 28% in those who received the midazolam. This study mitigated some of the hypotheses that its role was tied in its mind-altering effects, rather than its unique MOA as an NMDA receptor

modulator, furthering its promise as a novel treatment option for TRD.

A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes, reported by Mcgirr et al. concludes that single administrations of ketamine are efficacious in the rapid treatment of unipolar and bipolar depression. Additional research is recommended to determine optimal dosing schedules, route, treatment schedules, and the potential efficacy of other glutamatergic agents.<sup>15</sup>

**Table 1.** Characteristics of included studies

Study	Design	Diagnosis	Sample size	Instrument	Depression score	Placebo comparator	Ketamine dose	Follow-up period	Age (mean±s.d.)	Sex
Berman <i>et al.</i> (2000)	Cross-over RCT Double-blind	MDD(8)+BD(1)	9	HAMD-25	29.61±2.21	Saline	0.5 mg/kg 40 min infusion	3 days	37±10	5F/4M
Zarate <i>et al.</i> (2006)	Cross-over RCT Double-blind	MDD	18	HAMD-21	24.90±1.57	Saline	0.5 mg/kg 40 min infusion	7 days	45.86±11.80	12F/6M
Diazgranados <i>et al.</i> (2010)	Cross-over RCT Double-blind	BD	18	MADRS	32.60±1.09	Saline	0.5 mg/kg 40 min infusion	14 days	47.90±13.10	12F/6M
Zarate <i>et al.</i> (2012)	Cross-over RCT Double-blind	BD	15	MADRS	34.00±1.99	Saline	0.5 mg/kg 40 min infusion	14 days	53.90±3.27	8F/7M
Sos <i>et al.</i> (2013)	Cross-over RCT	MDD	30	MADRS	23.06±0.93	Saline	0.54 mg/kg; 0.27 mg/kg bolus and 0.27 mg/kg 20 min infusion	7 days	43.72±2.26	15F/15M
Murrough <i>et al.</i> (2013)	Double-blind RCT Double-blind	MDD	73	MADRS	32.07±0.69	Midazolam	0.5 mg/kg 40 min infusion	7 days (with additional 4 weeks in responders)	45.44±1.47	37F/36M
Lapidus <i>et al.</i> (2014)	Cross-over RCT Double-blind	MDD	20	MADRS	IDS-C 42.7±8.5	Saline	50 mg intranasal	7 days	48.0±12.8	10F/10M

RCT, Randomized controlled trial; MDD, major depressive disorder; BD, bipolar disorder; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; IDS-C, Inventory of Depressive Symptoms – Clinician rated; F, Female; M, Male.

## Drawbacks and Concerns

Over the decades numerous studies, such as the above, have been published supporting the conclusion that ketamine does in fact seem to improve TRD in as little as two hours with effects lasting for several days up to a few weeks. Other studies successfully trialed repeat IV infusions of ketamine followed by as needed maintenance doses for providing longer term relief of TRD.<sup>16</sup> Even so, valid concerns remain regarding the potential for abuse, psychotomimetic

side effects, and its long-term safety profile. Nonetheless, one may argue that reliance upon low, subanesthetic doses in ketamine therapy for depression would safeguard against these concerns.<sup>17</sup> Currently, trials and research persevere in studying these effects and in establishing the best route and dose of administration of ketamine to safely and effectively treat TRD. In a systematic review and meta-analysis of ketamine and other NMDA receptor antagonists in the treatment of MDD by Newport et al., it was concluded that 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.<sup>17</sup> Still, off-label use of ketamine for patients with TRD continues to rise in the US, where it's estimated approximately 60-100 ketamine clinics currently operate.<sup>18</sup>

### **Conclusion**

The predominant findings suggest that ketamine does, in fact, prove to be effective in rapid improvement of symptoms in patients with TRD. As more research continues to emerge, new questions arise. These questions vary from the potentials for abuse, long term side effect profile, best route and dosage of administration, the exact mechanism of action, et cetera. Although ketamine has been proven to have rapid and robust antidepressant effects, often apparent within hours post infusion, its effects seem to rarely persist longer than 2 weeks.<sup>15</sup> Studies demonstrating that ketamine's antidepressant effects can be sustained with serial infusions are lacking.<sup>15</sup> This deficiency would be an excellent area of future investigation. Further research may be necessary to elucidating the exact mechanism of action that works on reversing symptoms of TRD. While the research community resumes its search for answers to these questions, patient's with TRD continue to suffer. It is estimated about 5 to 6 million people have depression which is resistant to conventional pharmacologic, psychological or somatic

treatments.<sup>19</sup> Clearly ketamine has a role in clinical practice where it is already being used off-label in up to 100 ketamine clinics in the United States today. However, these clinics are often private ones where wealthy patients who can afford this off-label treatment are willing to pay high costs for these infusions, which health insurance does not cover.<sup>18</sup> Unfortunately, these costs are out of reach for most patients.

As pharmaceutical companies continue their search for the most effective approach to utilizing the antidepressant effects of ketamine, people continue to suffer from inadequately treated depression and chronic suicidality.<sup>20</sup> It is important to evaluate what we know of ketamine's effects and its potential in patients with TRD who experience suicidal thoughts or attempts. In 2017, a meta-analysis written by Wilkinson et al.<sup>21</sup> showed ketamine has a role in reducing suicidality, independent of its effect of improving depression. Many of those who are diagnosed with TRD also suffer with chronic suicidality. As a result, these people are often seen in an emergency room setting and either sent to a psychiatric facility or advised to follow up with their primary care doctors to be prescribed medications that don't take effect for weeks, sometimes months. The field of emergency medicine has much to gain by the use of this fast-acting antidepressant. In an article published by the Emergency Medicine Resident Association (EMRA), residents report their experience, "The unsettling reality is that the dearth of acute interventions means we discharge many of our depressed patients home without first being able to significantly reduce their symptoms. This is particularly worrisome in light of data suggesting that the risk of suicide increases immediately after discharge. But it doesn't have to be this way".<sup>22</sup> Although we are still years away from an outpatient approval of ketamine, it may be

time to consider the role of ketamine in emergency medicine for patients at immediate risk of suicidality.

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