Ketamine: An Underutilized Response to Treatment Resistant Depression

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by

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Abstract

This paper was inspired by an 18-year-old female patient that suffered from treatment resistant depression (TRD) amongst other psychiatric comorbidities. She failed multiple medication trials, psychotherapy modalities, residential treatments and electroconvulsive therapy (ECT) sessions, which left her healthcare team considering unorthodox treatment methods like ketamine. This paper explores published literature over the last 8 years on the research of administration of intravenous (IV) ketamine infusions for people suffering from TRD and acute suicidal ideation. The evidence shows that ketamine has rapid-onset antidepressant effects and can greatly reduce thoughts of suicide and many other depressive symptoms within hours of treatment, if the participant has an adequate response and is able to tolerate the medication. Ketamine infusions should be considered for patients suffering from TRD or those that are acutely suicidal. There continues to be a need for more research on its long-term effects, dosing frequency, the optimal patient, and its clinical monitoring.
**Background**

Suicide prevention and major depressive disorder are becoming more and more prevalent with social media outlets in today’s world. Major depression is the leading cause of disability in the United States, affecting more than 16.1 million American adults. More people are seeking help and treatment for their depression but sometimes medications and psychotherapy modalities are not enough, leading to TRD. Patients that have failed multiple medication trials, therapies, residential facilities, and ECT treatments have limited choices for treatment of their depression. Unfortunately there are not many options other than to consider something unorthodox and innovative, perhaps something like ketamine.

Ketamine is a medication best known for its general anesthetic effects, but more research is coming out proving its efficacy as a rapid-onset antidepressant. Having ketamine administered IV over 40 minutes can greatly reduce symptoms of depression and feelings of suicidal ideation within hours while other treatment modalities often take weeks to produce similar results. There is evidence to support using IV ketamine for acutely suicidal patients, but more research is needed in terms of it being a long-term option for TRD. This report will examine studies completed regarding IV ketamine for acutely suicidal patients and those treated for TRD.

**Case Report**

This report is based on a patient that was hospitalized multiple times on an inpatient psychiatry unit. She was an 18-year-old Caucasian female that required hospitalizations for acute suicidal ideation and multiple failed suicide attempts. She slept up to 18 hours a day, had anhedonia, chronic passive thoughts of wanting to kill herself,
no energy, was very distractible, and had stopped eating. Her affect was flat, she could barely whisper, and was catatonic at times. The patient reported being medication adherent with her 80 mg fluoxetine, 1,800 mg lithium, and 1,200 mg n-acetylcysteine daily doses. She was diagnosed with severe TRD, borderline personality disorder, anorexia nervosa, generalized anxiety disorder, obsessive-compulsive disorder and dependent personality disorder.

Her psychiatric history included a total of 52 psychiatric hospitalizations at an urban acute psychiatric facility. There were many other psychiatric hospitalizations she has had at other facilities that prior history or records could not be found. She attended 2 residential treatment facilities for 1 month long stays for her chemical dependency. She received individual psychotherapy sessions weekly and had group dialectical behavior therapy (DBT) sessions each week. This patient had failed medication trials of sertraline, fluvoxamine, escitalopram, venlafaxine, duloxetine, buspirone, bupropion, aripiprazole, lamotrigine, and valproic acid in the past. She also has had over 70 right unilateral ultra brief sessions of ECT and 15 bilateral brief ECT treatments within the last 2 years.

In terms of medical conditions, she had a history of seizures that were likely due to her anorexia nervosa. In regards to her social history, this patient was an only child living in a small town of 78 people in a rural state. She worked as a certified nursing assistant at a nursing home in a nearby town. Her parents were divorced and she lived with her mother who worked long hours as a floor nurse. Patient reported having a few good friends that would often drink alcohol and smoke marijuana together. She stated they would binge drink alcohol on the weekends and smoke marijuana multiple times a day after school throughout the week.
Patient’s laboratory values were consistent with what one may expect for someone diagnosed with anorexia nervosa. Her body mass index was 16. Her white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets, glucose, total protein, albumin, calcium, potassium, magnesium and BUN levels were all below normal values. She had an EKG that yielded normal results. Her pulse, blood pressure, and temperature were low but her oxygen saturation and respirations were typically normal when vital signs were assessed. Her lithium level was sub-therapeutic at 0.5 mmol/L upon admission to the unit.

Given her history of present illness and psychiatric history, the treatment team wanted to focus on improving the patient’s severe TRD and eating disorder. The immediate goals were to get rid of the patient’s acute suicidal ideation and improve her appetite so she could stabilize during her stay on the inpatient unit. Collaboration was done with the psychiatry director of the eating disorder unit to work towards getting the patient to eat at least 1,000 calories each day without causing refeeding syndrome, particularly with her low magnesium level. Due to her acute suicidality and sub-therapeutic lithium level, her lithium dose was increased to 2,400 mg. She has experiences memory deficits after bilateral brief ECT in the past. Because of the history of memory problems with ECT, the team ruled out having additional ECT treatments.

The team looked at research for ketamine as a potential treatment option for the patient’s active suicidal ideation and TRD. While the intervention for ketamine to treat depression literature was reviewed for efficacy, the patient started to stabilize. She began eating again and her active suicidal thoughts returned to her chronic passive suicidal thoughts. She continued to work on psychotherapy modalities and was adherent with her
medications. Though the patient stabilized, the team continued to look at IV and intranasal ketamine as a treatment option for the patient in future acute episodes of suicidality. Even though the team is continuing to work towards establishing a protocol for using ketamine as a treatment intervention, the evidence was reviewed to support the use of ketamine for acute suicidal ideation and TRD.

**Literature Review**

As suicide prevention and understanding major depressive disorder are becoming more prevalent in the mainstream media, it is more important than ever for those in psychiatry to understand its treatment and to stay current with new modalities. We already know Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for general anesthesia due to its dissociative effects and change of sensory perception.

The neurobiology of the mechanism of action for ketamine to treat depression was reviewed. One theory discusses chronic stress pathology (CSP) in the prefrontal cortex (PFC). According to Abdallah, Sanacora, Duman & Krystal (2018), the synaptic CSP model proposes that synaptic dysconnectivity may be a common pathological pathway across psychiatric disorders with chronic stress components-as a predisposition, a trigger, or an outcome. In the PFC, chronic stress is believed to induce glial deficit, leading to reduced glutamate reuptake capacity and increased extrasynaptic glutamate levels and excitotoxicity (Abdallah et al., 2018). Then, neuronal atrophy develops which results in overall reduction in glutamate neurotransmission and in the remaining PFC synapses the neurotransmission strength is also affected by reduced postsynaptic glutamate NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors
(Abdallah et al., 2018). It is thought that Ketamine reverses this PFC CSP within 24 hours of injection and induces a transient postsynaptic glutamate activation, which leads to upregulation of neurotrophic signaling, increased protein synthesis, and sustained (days-to-weeks) restoration of synaptic connectivity (Abdallah et al., 2018). The mechanism of action of ketamine therefore creates antidepressant effects. Evidence was reviewed to determine how to avoid ketamine’s anesthetic doses as well as its requirements prior to administration for acute suicidality and TRD.

The U.S. Department of Veteran Affairs (VA) (2017) worked with the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments to review the literature on the use of ketamine infusion for TRD and severe suicidal ideation to provide a protocol on its general administration (VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, & Office of Mental Health Somatic Treatment Field Advisory Committee, 2017). The first portion of their protocol consists of inclusion and exclusion criteria. Inclusion criteria consists of a patient with a current diagnosis of major depressive disorder (MDD), the patient has failed to achieve a full response to 2 adequate therapeutic trials of antidepressants including augmentation or severe suicidal depression for which a rapid treatment onset is important, a psychiatric evaluation, legal informed consent, and transportation home after the infusion (VA Pharmacy Benefits Management Services et al., 2017). There are screening requirements that must be completed within 30 days before the administration of ketamine, which includes reviewing the inclusion criteria, PHQ-9, Montreal Cognitive Assessment tool (MoCA) (designed to rapidly screen for mild cognitive dysfunction.), physical examination with vitals, relevant laboratory
measures, urine toxicology, pregnancy screens and the review of concurrent use or abuse of CNS depressants (VA Pharmacy Benefits Management Services et al., 2017). The ketamine is administered IV at 0.5 mg/kg (based on the patient’s body weight) using an infusion pump over 40 minutes with vital signs assessed at onset, 10, 20, 30, 40, 80, 110, and 240 minutes (VA Pharmacy Benefits Management Services et al., 2017). According to the VA Pharmacy Benefits Management Services et al. (2017), the ketamine infusions should be repeated no less than 3 days apart and not more frequently than twice a week for 2-3 weeks with the goal to extend the interval between infusions to as long as possible (usually monthly). Ketamine treatment should be discontinued or considered a failure if the patient needs to have the infusion stopped more than once due to exceeding the blood pressure or heart rate thresholds, after having 4-6 infusions without an adequate response (defined as 50% or greater decline in the PHQ-9 score from baseline), if slow to correct cognitive impairment (MoCA) or repeated dissociative symptoms, or when dosing cannot be spaced out to a minimum of 1 dose per week by the second month of treatment (VA Pharmacy Benefits Management Services et al., 2017). This national protocol was established because there is evidence that confirms that ketamine improves the symptoms of TRD and alleviates acute suicidal ideation.

A randomized clinical trial by Grunebaum et al. (2018) compared an adjunctive infusion of ketamine compared with the short-acting midazolam for patients with MDD who had clinically significant suicidal ideation. 82 participants that ranged between 18-65 years old were randomly assigned to receive IV ketamine hydrochloride at 0.5 mg/kg or midazolam at 0.02 mg/kg in 100 mL normal saline infused over 40 minutes. The results showed that those that received the ketamine infusion, adjunctive to ongoing
pharmacotherapy, were associated with a greater reduction in suicidal thoughts at day 1 compared to those that received the midazolam infusion (Grunebaum et al., 2018). It was also noted that the decreased suicidal ideation in this trial was largely maintained through the 6-week follow-up ratings, which was quite interesting since many studies typically only see these effects last for 1-2 weeks (Grunebaum et al., 2018). Grunebaum et al. (2018) also found greater reductions in overall mood disturbance, depression, and fatigue on day 1 for those that received ketamine compared to midazolam.

In a study by Murrough et al. (2013), ketamine and midazolam were compared. This study completed a two-site randomized controlled trial of a single infusion of ketamine compared to the active placebo midazolam. 73 patients with TRD that were actively experiencing a depressive episode were randomly assigned under double-blind conditions to receive the infusions (Murrough et al., 2013). According to Murrough et al. (2013), the primary outcome would be using the Montgomery-Asberg Depression Rating Scale (MADRS) 24 hours after drug administration. MADRS is a ten-item diagnostic questionnaire that providers use to measure the severity of depressive episodes in patients with mood disorders by assessing apparent and reported sadness, reduced sleep and appetite, concentration difficulties, inability to feel, pessimistic thoughts and suicidal thoughts. The questionnaire of the MADRS has a scale from 0 to 6 for each symptom with 6 being the most extreme. Therefore, the higher the MADRS score means the more depressed the individual is. The results of the study showed that the MADRS scores were lower by 7.95 points in the ketamine group than in the midazolam group at 24 hours post-infusion (Murrough et al., 2013). The authors had participants complete a self-report at 7 days post-infusion regarding their depression and it was found that there was no
significant difference between treatment groups (Murrough et al., 2013). The data supported that NMDA receptor modulation can accelerate clinical improvement in patients with severe and chronic forms of depression but the study had limitations in needing to have stringent enrollment criteria due to concerns about ketamine’s psychoactive effects and abuse liability (Murrough et al., 2013). For this study, patients were excluded if they had a history of alcohol or substance abuse in the previous 2 years but no other criteria was noted for screening substance use disorders.

A systematic review and individual participant data meta-analysis by Wilkinson et al. (2018) was completed regarding patients that had single-dose IV ketamine with comparisons of either saline placebo or midazolam for the treatment of any psychiatric disorder with suicidal ideation. Wilkinson et al. (2018) found that ketamine significantly reduced suicidal ideation, with moderate to large effect sizes observed within 1 day that extended 1 week after ketamine administration. Results found 54.9% of patients were free of suicidal ideation 24 hours after a single ketamine infusion and 60.0% were free of suicidal ideation at 1 week post-infusion (Wilkinson et al., 2018). According to Wilkinson et al. (2018), ketamine’s effects on suicidal ideation were partially independent of its effects on mood, although subsequent trials in transdiagnostic samples are required to confirm that ketamine exerts a specific effect on suicidal ideation.

Feifel, Malcom, Boggie & Lee (2016) completed a retrospective analysis of the safety and efficacy of the initial ketamine infusion administered to a cohort of patients. The inclusion and exclusion criteria of clinical studies investigating ketamine’s antidepressant effects have become less stringent or have suicidal ideation as an inclusion requirement rather than an exclusion criteria, therefore Feifel et al. (2016) wanted to
investigate ketamine’s efficacy in patients more representative of the TRD population. There were no formal criteria for treatment with ketamine in their study. Psychiatrists had to refer candidates for IV ketamine treatment and participants were generally deemed to be appropriated if they were experiencing severe depression that significantly reduced their quality of life or placed them at significant risk of suicide, they had failed to respond to several trials of medications in the current episode despite an adequate dose and duration (at least four weeks) or due to intolerance of medication (Feifel et al., 2016). Some patients had failed ECT or rTMS and some chose not to participate due to a history of a psychotic disorder, uncontrolled hypertension, a previous adverse reaction to ketamine, significant active medical conditions, active substance use, pregnancy or breastfeeding (Feifel et al., 2016). However 73% of participants did have a psychiatric comorbidity (Feifel et al., 2016). The participating patients had ketamine infused over 40 minutes at a dose of 0.5 mg/kg based on the patient’s actual body weight on the day of the infusion (Feifel et al., 2016). They were asked to complete a Beck Depression Inventory (BDI) prior to their infusion, approximately 1 hour post-infusion, 24 hours post-infusion, and were asked to document in a narrative fashion any changes in their mental state since the infusion (Feifel et al., 2016). According to Feifel et al. (2016), their results showed that a single infusion of low-dose ketamine is efficacious and generally well tolerated in the sample population treated in a ‘naturalistic’ clinical context. Average pre-infusion BDI scores were 32.6 and dropped to 16.8 at 24 hours post-infusion (Feifel et al., 2016). Feifel et al. (2016) study had limitations such as that the study reported retrospective data, there was a lack of a control group, and self-report depression rating scales were utilized for evaluation.
A study by Singh et al. (2016) evaluated the efficacy of twice- and thrice-weekly IV administration of ketamine in sustaining initial antidepressant effects in patients with TRD. In this double-blind study, 67 patients ages 18-64 with TRD were randomized to receive either IV ketamine (0.5 mg/kg of body weight) or intravenous placebo, administered over 40 minutes, either two or three times weekly, for up to 4 weeks (Singh et al., 2016). The primary outcome measure was change from baseline to day 15 in total score on the MADRS (Singh et al., 2016). According to Singh et al. (2016), in the twice-weekly dosing groups, the mean change in MADRS score at day 15 was -18.4 for ketamine and -5.7 for placebo and in the thrice-weekly groups it was -17.7 for ketamine and -3.1 for the placebo. Though some participants experienced side effects of anxiety, dissociation, headache, nausea, and dizziness, the results of the study concluded that both the twice-weekly and thrice-weekly administration of ketamine maintained antidepressant efficacy over the 15 days (Singh et al., 2016).

Like the last authors, aan het Rot et al. (2010) were interested in the tolerability, safety and efficacy of repeated-dose open-label IV ketamine (six infusions over 12 days) in 10 medication-free symptomatic patients with TRD. This study was interesting because these 10 patients had already previously shown a meaningful antidepressant response to a single dose of ketamine. The study was set up so participants received ketamine 0.5 mg/kg per body weight infusion over 40 minutes on day 1 and a MADRS score was taken on day 2. If their scores showed a >50% reduction in MADRS scores, they were able to receive five additional infusions on days 3, 5, 8, 10, and 12. Nine participants were able to have all six infusions with a result of a reduction in MADRS scores being 85% after the sixth infusion (aan het Rot et al., 2010). Post ketamine
infusions, eight of nine patients relapsed with the average being 19 days after the sixth infusion (aan het Rot et al., 2010). Of note, they ranged from 6 days to 45 days and one patient was antidepressant-free with minimal depressive symptoms for greater than 3 months (aan het Rot et al., 2010).

Like the last study, a study completed by Murrough et al. (2012) wanted to examine the pattern and durability of antidepressant effects of repeated ketamine infusions. Murrough et al. (2012) had 24 people with TRD complete two phases, with the first phase undergoing a washout of antidepressant medications followed by a series of up to 6 IV infusions of ketamine at 0.5mg/kg of body weight administered open-label three times weekly over a 12-day period. In the second phase, participants who met response criteria following the last dose of ketamine in phase 1 were followed until relapse or for the maximum follow-up time of 83 days, whichever came first (Murrough et al., 2012). Of note, response in phase 1 was defined as a >50% improvement in depressive symptoms as measured by MADRS and relapse in phase 2 was defined as <50% improvement in MADRS score at that visit compared to baseline for two consecutive visits (Murrough et al., 2012). 24 participants received at least one ketamine infusion, 22 participants received at least two infusions, and 21 participants received all six scheduled ketamine infusions (Murrough et al., 2012). Of the three that did not complete all six infusions, one had non-response per protocol of MADRS scores, one experienced hemodynamic elevation during the first infusion, and the other withdrew following three infusions due to perceived lack of response (Murrough et al., 2012). According to Murrough et al. (2012), the overall response rate at the end of the study was 70.8% with there being a large statistically significant mean improvement in MADRS at two hours
following the first ketamine infusion (decrease from 31.8 to 12.9). The median time to relapse following the last ketamine infusion was 18 days so it appeared to have a rapid antidepressant effect in patients with TRD, which was a predictive of a sustained effect (Murrough et al., 2012).

**Implications**

Based on the literature review, there is a significant amount of evidence that administering 0.5mg/kg per body weight of IV ketamine over 40 minutes to a patient with acute suicidal ideation or TRD will decrease their depressive symptoms and reduce their suicidal thoughts. Both MADRS and BDI scores, which each measure the severity of depressive symptoms, improved rapidly after the administration of the medication. Therefore, it is reasonable to consider trying ketamine for patients with TRD or acute suicidal ideation.

Patients similar to the one described in the initial patient case report discussed are great candidates as to the type of person that would benefit from IV ketamine administration. For the patient case report previously discussed, ketamine is an option the treatment team will highly consider should she become hospitalized in the future. Again, though the treatment team is continuing to work towards establishing a protocol, the evidence reviewed does support the use of ketamine for acute suicidal ideation and TRD.

Each study reviewed in this report varied whether it was the type of study completed, a single infusion of ketamine, or repeated dosing with varying frequencies. Regardless, all studies recommend further research for using ketamine as a treatment intervention in depression. Although there is evidence that proves ketamine infusions provide rapid antidepressant effects, there continues to be a need for more research on
optimal patient inclusion criteria, dosing frequency, clinical monitoring, and follow-up assessment periods. Though this case study report consists of literature featuring ketamine infusions beyond a single dose, there is still a need for more evidence beyond six infusions to develop a longer-term safety profile.

Further research should include studies specific to comparing ketamine to ECT or lithium in terms of their reduction for suicidal ideation. Although the VA (2017) created a national ketamine protocol, there are still plenty of other facilities and clinics that have their own protocols. Comparing the various protocols is another component of ketamine administration for TRD and suicidal ideation that could be further researched and evaluated perhaps by a psychiatric mental health nurse practitioner (PMHNP).

PMHNPs can be a part of the growing evidence for ketamine administration for TRD and acute suicidality by being aware of the medication as a treatment option for their patients. PMHNPs should know that review of the evidence confirms that ketamine has rapid-onset antidepressant effects for patients with acute suicidality and TRD. Ketamine clinics are becoming more available, therefore it is easy for patients to go to a clinic to try it for themselves without a psychiatrist or PMHNP prescribing or evaluating their care initially. Due to this, PMHNPs should be aware of ketamine clinics that are available in their communities, review ketamine protocols, and consider whether ketamine clinics should be an option for their patients with acute suicidal ideation or TRD. PMHNPs can consult with other providers and make referrals to ketamine clinics if their patients have failed multiple medication trials, psychotherapy modalities, residential facilities, and ECT treatments.
It would be important for PMHNPs to ensure their patients are aware of the potential side effects and to tell their patients that there is not much evidence for ketamine administration for TRD and acute suicidality in terms of its long-term effects and safety profile. The patients that are interested in ketamine infusions for TRD should know common side effects include sedation, nausea, vomiting, dizziness, drowsiness, confusion, hallucinations, and anxiety. Murrough et al. (2012), Singh et al. (2016), Grunebaum et al. (2018), aan het Rot et al. (2010), (Feifel et al., 2016), and Murrough et al. (2013) all mentioned that their participants experienced these side effects to a minor degree.

Patients should also be aware that ketamine is still a novel idea in psychiatry so there is a need for further research with its long-term efficacy and frequency of dosing. Though more research is needed, it is reasonable for a PMHNP to recommend ketamine infusions as a treatment option for TRD or acute suicidality. PMHNPs can also further advance the evidence for ketamine for TRD and acute suicidal ideation by assisting with future research studies and by working with other providers to develop a standardized protocol with specific inclusion and exclusion criteria for administration of the medication.
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