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# Ketamine: The Potential for Treatment Resistant Depression

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by

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# PERMISSION

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## Abstract

A 42- year old woman with treatment resistant depression was admitted to a psychiatric facility for suicidal ideation. Her depressive symptoms have been persistent for the past 5 years with no relief using any of the mainstream anti-depressant treatments. The patient was unable to function in life and was basically catatonic. Prior to the onset of depression, the patient was a highly functioning mother of five, with no history of depression. The woman was included in a clinical trial of intravenous ketamine treatments for severe depression at the Mayo Clinic in Rochester, MN and after the second treatment, the woman's depression lifted. The psychiatrist that had been treating her said it was like she was a different person. There have been multiple controlled trials that have demonstrated a rapid, non-sustained, anti- depressive effect to a single, low dose of intravenous ketamine. The anti-depressive effects have been shown to last one to four weeks, so the treatments need to be on-going. Ketamine infusions require monitoring which limit ketamine's ability to be widely used in patients that suffer from treatment resistant depression. More research is needed in all areas of the use of ketamine for treatment resistant depression so that it can become more main stream and enable all mental health providers to feel comfortable prescribing it.


## Background

Currently, treatment of major depressive disorder (MDD) and bipolar depression is with pharmacotherapies that often take weeks before they are therapeutic. Furthermore, the efficacy of the current antidepressants is limited. The approved antidepressant medications work on the monoaminergic mechanisms with varying degrees of affinity for serotonin, dopamine, and norepinephrine. Recently, the glutamate system has been receiving more attention as a new way

for developing therapeutics for MDD. This attention has stemmed from the rapid and effective antidepressant effects of subanesthetic infusion of ketamine. Ketamine's clinical efficacy has led to many clinical studies to further explore the glutamatergic mechanisms and its role in depression (Iadarola et al., 2015).

## Case Report

Presenting patient problem: A 42- year old woman was admitted to an inpatient unit for major depressive disorder and suicidal ideation. History of present psychiatric illness: The psychiatrist started treating her when she was 38 years old which is when the depression started. Prior to this, the patient did not have any depressive symptoms. The patient had no medical issues other than a low B12 level which she was receiving B12 injections for. The patient's family history included two sisters that suffered from post- partum depression, but the patient did not experience any depressive symptoms post-partum. The psychiatrist tried numerous antidepressants, combination of antidepressants, and ECT (both bilateral and unilateral) with little to no response. The patient remained catatonic. Prior to this depressive episode, the patient was a highly functioning mother of five children. The patient and her husband had three children of their own and then adopted two boys from Haiti. The patient was unable to care for her children and would stay in her bedroom all day. She was in and out of the hospital due to suicidal thoughts for approximately four years. Approximately a year ago, the patient was included in a clinical trial at Mayo Clinic that included ketamine for treatment resistant depression. The first treatment helped the patient, but the second treatment helped tremendously. The psychiatrist said when the patient came back to him after the treatment, she was like a completely different person. The patient was energetic, made eye contact, and was excited to start living her life. When the trial was over, the patient was frantic to find a place where she

could continue the treatments. She could start to feel the depressive symptoms return around week 3 post-treatment. A psychiatrist in Duluth agreed to continue the patient's ketamine treatments. The patient drove approximately five hours each way every three weeks for the treatments. The patient stated that if she did not continue the treatments, she was sure she would have committed suicide. The psychiatrist in Duluth that provided the ketamine treatments retired recently and now the psychiatrist in her home community is prescribing the ketamine treatments. The psychiatrist did extensive research on the topic and was a bit apprehensive to begin the treatments, but due to the severity of this patient's depression and the remarkable results from the ketamine treatments, he agreed to do this for her. Since he has started the treatments for this patient, he has been getting calls from many other psychiatrists requesting that he treat their patients, but he isn't going to do this since it is quite time consuming to administer the treatments. The psychiatrist has it set up now where he only needs to be present at the beginning of the treatment and a nurse anesthetist administers it for approximately 45 minutes. The psychiatrist stated that the patient falls into a dream-like state during the treatments which makes her feel as if she is floating, which she describes as pleasant. The patient tolerates the treatment very well. The only side effect that she has is some numbness and tingling around her lips for a few minutes after the treatment. The patient is able to eat and drink after the treatment. She is not supposed to drive but the psychiatrist thinks she probably could drive without a problem. The patient is currently receiving treatments every three weeks. Since the patient started the ketamine treatments, she developed breast cancer and was able to get through the breast cancer treatments, which included a double mastectomy and reconstructive surgery without it affecting her mental health. The psychiatrist stated that he does not believe she would have made it through the breast cancer treatments if she had not been receiving the ketamine treatments.

Since the patient has been receiving the ketamine treatments, she has started a support group for patients suffering from depression, she is heavily involved in volunteering for the Special Olympics, and she started exercising regularly.

## Literature review

Major depressive disorder (MDD) is a significant public health issue. Current treatments for MDD target monoamine-targeting agents with limited efficacy. It is estimated that the medications that target the monoamine system provide relief for approximately 54% of patients (DeWilde, Levitch, Murrough, Mathew, & Iosifescu, 2015). Currently, there are over 30 medications that are approved for the treatment of depression. The antidepressants are categorized under various families, but they all are similar in their mechanism of action on one or more of the brain's monoamine neurotransmitters which include serotonin, dopamine, and norepinephrine. Recently, research has looked at the glutamate system as a potential antidepressant target. Ketamine directly regulates glutamate neurotransmission (the primary excitatory neurotransmitter in the brain) by acting as a noncompetitive N-methyl-Daspartate (NMDA) receptor antagonist. Ketamine is currently used as an anesthetic agent and is also used off label for chronic pain. Ketamine has been shown in clinical trials to act rapidly on MDD. The effects of Ketamine can be seen in as little as 40 minutes after IV infusion and can last 3-7 days. Repeated infusions have been studied with a response rate of 70.8% at the end of the study. Intranasal ketamine administration is also being investigated since IV administration is not as convenient (DeWilde et al., 2015).

This positive response gives hope that with further research into ketamine, it may be used more often for those patients that are resistant to the current antidepressant treatments. When a patient is having suicidal ideation, this could be an effective, rapid acting treatment. Recently,

there have been more reports of ketamine's unique antidepressant effects which have sparked more media coverage of the potential benefits for patients that suffer from treatment resistant depression. This increase in interest, and possible help for patients, families, and clinicians that deal with treatment resistant depression, has led to a demand for access to ketamine treatments and an increase in clinicians willing to administer ketamine treatments. Many in the field of psychiatry are cautious due to the small sample size in the studies done thus far. Another reason for caution is that the treatment has not been approved by the US Food and Drug Administration for on label use (Sanacora et al, 2017).

Sanacora et al. (2017) noted that The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatment found that as of 2017, there had been 7 published studies that included placebo-controlled, double-blind randomized control studies on ketamine infusion therapy in the treatment of major depressive disorder. The consensus of the 7 studies found that there is compelling evidence that the use of ketamine infusions is a rapid and effective treatment for treatment resistant depression. Nine meta-analysis of randomized acute-phase, short term trials of ketamine for depression have shown statistically significant improvement in depressive symptoms (Bobo, 2016). More studies are needed on the use of ketamine in psychiatric patients. Ketamine has been used for over 45 years as an anesthetic agent, but up until recently, there were no studies done on the safety and effectiveness in the use of patients suffering from depression (Sanacora et al., 2017). There are no current guidelines outlining the training and qualifications of a provider to administer the low doses of ketamine for treatment resistant depression (Sanacora et al., 2017).

Recently, two meta-analysis were done, and both support the rapid antidepressant and anti-suicidal efficacy of a single ketamine infusion treatment for both unipolar and bipolar

depression (Kishimoto et al., 2016; Wilkinson et al., 2018). These reviews found that there was a gradual loss of the antidepressant effect which ranged from a day to a week after a single dose of ketamine. This has led to repeated ketamine infusions so that the antidepressant effect can be extended.

Zheng et al. (2018) investigated the effect of repeated doses of ketamine. An open-label study was done on 97 Chinese patients with unipolar or bipolar depression (Zheng et al., 2018). Six repeated doses of ketamine were utilized. The results revealed a 68.0% response rate and a 50.5% remission rate which is much better than the results seen with the single ketamine infusion studies that resulted in a 50.0% response rate and 29.4% remission rate (Zheng et al., 2018). The six ketamine infusions were found to be safe with the only side effect being mild dissociative symptoms which returned to baseline after the first infusion (Zheng et al., 2018).

**Intranasal Esketamine Treatment**

Another promising treatment is the use of Esketamine. Esketamine is the S-enatiomer of ketamine and is being developed as an intranasal formulation to be used in treatment resistant depression and suicidal ideation (Daly et al., 2017). Intravenous administration of ketamine reduces its applicability in settings that are not staffed by trained anesthetists. In the first randomized clinical trial that measured the efficacy and safety of intranasal esketamine in the treatment of treatment-resistant depression, it was found that it was effective in treating treatment resistant depression. Improvements in depressive symptoms continued for up to 2 months after stopping the esketamine dosing (Daly et al., 2017).

Further support for the use of esketamine is due to a double-blind, randomized, placebo-controlled study that was conducted over a 20-month period in 11 sites across in the United States by Canuso et al., 2018. The study drug was a nasal spray device that delivered either

14mg of esketamine or placebo. All participants were severely depressed and suicidal and were also receiving standard of care antidepressants. The results of this study showed that intranasal esketamine may be an effective treatment for the rapid reduction in depressive symptoms and suicidal ideation (Canuso et al., 2018). This is promising given that there is no approved medication that can manage the potentially lethal condition of suicidal ideation. Intranasal esketamine was well tolerated outside of reports from five of the patients in the esketamine group that experienced agitation, aggression, dizziness, dyspnea, unpleasant taste, and nausea (Canuso et al., 2018). Further studies need to be done on intranasal esketamine but this is a promising treatment for patients that are actively suicidal and severely depressed.

**Ethical considerations**

Ethical issues that surround the use of ketamine use in the treatment of depression include limited studies on the safety and efficacy of off-label use of ketamine, the need to treat patients with severe, treatment resistant depression and the potential of misuse of ketamine (Singh et al., 2017). Ketamine is available to be used off label for treatment resistant depression due to it being licensed drug (Singh et al., 2017). The use of off label medications is common, especially in the field of psychiatry due to many drug companies not pursuing indication from the Federal Drug Administration (FDA) for specific disorders. This leaves decision making to the clinician to base dosing, efficacy, and side-effect risks from clinical experience and case-studies. The randomized control trials that have been done do not take into consideration how patients interact with the treatments outside of the controlled trial process which is especially important when dealing with a drug that has the potential to abuse. Since ketamine is a generic drug, the likelihood of large, expensive trials on diverse populations is unlikely due to the lack of public funds available to conduct these trials (Singh et al., 2017).

This presents the dilemma that there are many people that are suffering from treatment resistant depression that are at high risk for suicide that could benefit from ketamine treatment. There is a case to be made for professional administration of ketamine treatment to patients with severe, treatment resistant depression. The potential for misuse and abuse of ketamine is significantly reduced if the patient is given a low dose by a medical provider. The potential for abuse is increased when the patient is able to self-administer via other routes (intranasal, transmucosal, oral, sublingual, and subcutaneous). Another area of concern is the potential for lower urinary tract symptoms with a long duration of ketamine use. Chen, Lee, Chen, Hu, & Lin, (2017) found that in treating depression with a long duration of ketamine treatment, there was a significant increase in risk of developing lower urinary tract symptoms, which included interstitial cystitis/painful bladder syndrome.

**Ketamine clinics**

Currently, it is unknown how many ketamine clinics are operating in the United States, but it is believed to range from 60-100 (Nemeroff, 2018). Many of these clinics do not follow the American Psychiatric Association task force recommendations in using ketamine for the treatment of depression. Several of these clinics are making unsubstantiated claims that ketamine can treat not only depression, but can also treat migraines, obsessive compulsive disorder, chronic pain, and post- traumatic stress disorder (Nemeroff, 2018). There is very little evidence that ketamine is effective at treating any of the other psychiatric diseases other than depression. Unfortunately, many of these clinics do not have a psychiatrist on staff, they do not perform a thorough psychiatric assessment, and they do not screen for drug and alcohol abuse (Nemeroff, 2018).

## Implications for practice

Severe depression can derail a person's life by taking away their will to live, ability to take care of their family, and in some cases, their ability to work. Severe depression can undermine autonomy due to low self-worth and the inability to identify authentic desires. Decision making in a severely depressed person can be affected due to the feeling that their life isn't worth living. Therefore, it is an ethical duty as a provider to protect a person's autonomy by providing treatment for depression.

It is a reasonable expectation that there may be harmful side-effects from treatment that need to be managed by the provider and patient. The treatment and the side effects need to be discussed with the patient, and together, an informed decision needs to be made by the patient on how to proceed with treatment. The capacity of patients that suffer from severe depression that are desperate for treatment has been questioned, but this should not be compared to a person that lacks capacity (Singh et al., 2017). In reality, most patients that suffer with severe depression are usually indecisive and more cautions, rather than risk taking. As psychiatric providers, it is our duty to educate patients on the potential treatments, benefits, side effects, and cost of a treatment. At that point, an informed decision needs to be made whether to proceed or not. Singh et al. (2017) suggests that to ensure best practice in relation to consent, one should consider a time interval between the education on treatment and first treatment. This allows time for the patient to reflect on their decision, get a second opinion, and discuss it with family. In practice, the patient should be provided a written consent that reviews the risks, benefits, and a clear explanation that there is a lack of data on the long-term risks of ketamine. The patient should also be informed of ketamine's misuse potential. The dose of intravenous ketamine that is being used for treatment of depression is very low and the potential for abuse is low due to it being

administered in the clinical setting. The ability to self-administer can help promote patient autonomy and compliance but the potential for misuse is also higher. If there are breakthrough depressive symptoms, the treatment is on hand for the patient to use higher and more frequent doses just like any of the addictive medications that are prescribed. It is up to the clinician to ensure that the patient is able to make an informed, autonomous decision on if they want to start treatment with ketamine. Clinicians that prescribe ketamine need to have a heightened degree of responsibility and need to monitor these patients closely.

Ketamine therapy has a promising depression treatment potential that will continue to develop. Unfortunately, if there is widespread abuse, this will be delayed, or stopped, due to concerns about the drug and decrease the public's trust (Singh et al., 2017). Further research is needed in all areas of the use of ketamine for depression. Some of the areas that need more research include long term data on the safety of repeat dosing of ketamine, clinical trials in naturalistic cohorts, incidence of misuse among the different forms of ketamine, and more innovative use of ketamine for the treatment of severe depression (Singh et al., 2017). As advanced practice psychiatric nurses, it is our duty to remain abreast of this research and to advocate for safe administration and monitoring of this promising treatment.

# References

Bobo, W.V., Vande Voort, J.L., Croarkin, P.E., Leung, J.G., Tye, S.J., Frye, M.A. (2016). Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. *Depression and Anxiety, 00,* 1-13.

Canuso, C. M., Singh, J. B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., & Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *American journal of psychiatry*, *175*(7), 620-630.

Chen, I. C., Lee, M. H., Chen, W. C., Hu, T. C., & Lin, H. Y. (2018). Risk factors of lower urinary tract syndrome among ketamine users. *LUTS: Lower Urinary Tract Symptoms*, *10*(3), 281-286.

Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., & Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA psychiatry*, *75*(2), 139-148.

DeWilde, K. E., Levitch, C. F., Murrough, J. W., Mathew, S. J., & Iosifescu, D. V. (2015). The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Annals of the New York Academy of Sciences*, *1345*(1), 47-58.

Feifel, D. (2016). Breaking sad: unleashing the breakthrough potential of ketamine's rapid antidepressant effects. *Drug development research*, *77*(8), 489-494.

Iadarola, N. D., Niciu, M. J., Richards, E. M., Vande Voort, J. L., Ballard, E. D., Lundin, N. B., & Zarate Jr, C. A. (2015). Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Therapeutic advances in chronic disease*, *6*(3), 97-114.

Nemeroff, C. B. (2018). Ketamine: Quo Vadis? *American Journal of Psychiatry* 175(4), 297-299,

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., Summergrad, P., & Nemeroff, C. B. (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA psychiatry*, *74*(4), 399-405.

Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., & McShane, R. (2017). Ketamine treatment for depression: Opportunities for clinical innovation and ethical foresight. *The Lancet Psychiatry*, *4*(5), 419-426.

Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., & Sanacora, G. (2017). The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *American journal of psychiatry*, *175*(2), 150-158.

Zheng, W., Zhou, Y. L., Liu, W. J., Wang, C. Y., Zhan, Y. N., Li, H. Q., Chen, L.J., Li, M.D., & Ning, Y. P. (2018). Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. *Journal of psychiatric research*, *106*, 61-68.