# Subanesthetic Intravenous Ketamine for Treatment- Resistant Depression

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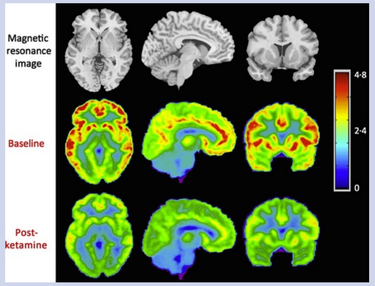
## Abstract

Treatment-Resistant Depression (TRD), a subset of Major Depressive Disorder (MDD) characterized by failure to respond to at least two antidepressants, is attributed to neuronal impairment; thus, anesthetic drugs (potent regulators of neuronal activity) may improve compromised neuroplasticity observed in psychiatric disease. It has been proposed that subanesthetic doses of intravenous Ketamine infusion may provide rapid antidepressant effects, either alone or as an adjunct to traditional antidepressants. Clinical trials investigating the legitimacy of Ketamine (a competitive N- methyl-D-aspartate (NDMA) receptor antagonist), in the treatment of TRD substantiate this possibility. Ketamine is believed to relieve anhedonia and reduce suicidal ideation, a feature that is particularly unique to this drug. Ketamine appears to be safe for IV administration in TRD patients as no significant complications have been reported. However, treatment with Ketamine is not without risk. While several considerations have not been addressed, experimental and clinical observations collectively present Ketamine as a viable therapeutic option for TRD.




Binding of ketamine to mGluR5 in brain, as demonstrated by displacement of the selective PET ligand

## Methods

Methods across the studies were comparable. Participants received up to six Ketamine infusions administered over 40 minutes over twelve-days. Patients were required to have a diagnosis of MDD as determined by the Structured Clinical Interview for DSMV, and an insufficient response to two or more antidepressant drug therapies. Patients with a history of bipolar disorder, psychosis, substance abuse, unstable medical conditions, suicidal or homicidal risk, or used contraindicated medications were excluded.

Each participant received a physical evaluation, standard biochemical and hematologic tests, urine toxicology assays, and an EKG to indicate medical illness or drug use. For the duration of the studies, the participants were free of concomitant psychiatric medications and were required to be drug-free for a minimum of four weeks before receiving their first infusion. Patients were assessed via a variety of tests including the the Montgomery-Asberg Depression Rating Scale (MARDS), Hamilton Rating Scale for Depression (HAMD), PHQ-9, and Scale for Suicide Ideation (SSI). Assessments were performed at baseline, during each infusion, 24 hours after the infusion, and each day following infusion for up to four weeks post-infusion.

## Review of Literature

Multiple studies have demonstrated that single doses of 0.5 mg/kg IV ketamine have antidepressant properties for up to 4 weeks; however, few research have investigated the effects of prolonged treatment. In a study of 24 patients with unipolar depression, 70.8 percent responded after six ketamine infusions, with an average duration of response of 18 days; response after six ketamine infusions was strongly predicted by response four hours after the initial infusion (Schwartz et al., 2016).

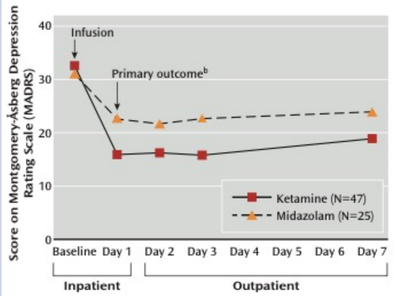
In a double-blind controlled study where patients received an infusion of either 0.5 mg/kg ketamine or 0.045 mg/kg Midazolam, patients in the ketamine group had significantly greater improvement in the MADRS score at 24 hours when compared to the Midazolam group. After adjustment for baseline scores, the average MADRS score was 7.95 points lower in the ketamine group than in the Midazolam group. However, statistically significant differences in MADRS scores, between the two groups, were not observed after 7 days (Murrough et al., 2013). For each additional day post- infusion, both groups demonstrated a worsening in MADRS scores (b=0.0004; 95% CI, 0.00009 to 0.00062). However, when the scores were collapsed across time, the ketamine group had lower MADRS scores (mean, 16.93; 95% CI, 14.03 to 19.82) than the Midazolam group (mean, 23.19; 95% CI, 19.03 to 27.34) (Murrough et al., 2013)

In studies using single dose of ketamine infusion demonstrate a higher rate of relapse was observed when compared to the rates from studies using continuous infusions. In two single dose, placebo-controlled studies, 92% of patients relapsed within 14 days (Aan het Rot et al., 2010).

The effect of ketamine on “Wish to Live” and “Wish to Die,” as measured by the SSI shows that in placebo- controlled trials, Ketamine infusion was associated with increased “Wish to live”, F1,393 ¼ 53.05, p < .001, and decreased “Wish to Die”, F1,389 ¼ 48.53, p < .001. However, the reduction in suicidal ideation diminished with time following the treatment (Ballard et al., 2014)

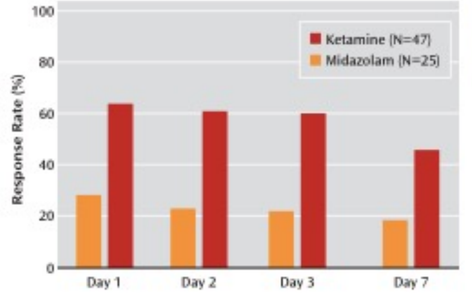
The most common adverse events in the ketamine group for up to 4 hours after infusion were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. These side effects occurred immediately after the Ketamine infusion and dissipated within 2 hours post-infusion. No severe psychotic symptoms (paranoia, hallucinations, delusions, or thought disorder) occurred in any patient. On average, mild transient changes in blood pressure were observed on the infusion day but no adverse hemodynamic events were reported.

**FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]**



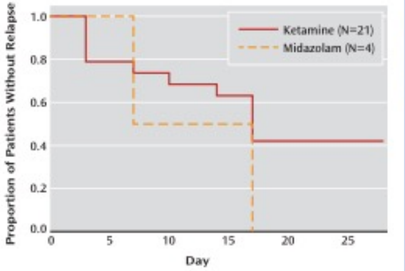

[a] Modified intention-to-treat group. MADRS scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.
[b] Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (p≤0.002).

**FIGURE 2. Response Rates Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]**

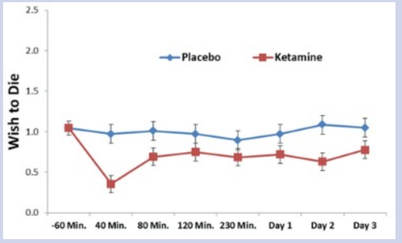


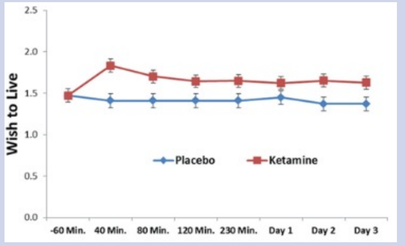

[a] Modified intention-to-treat group. Response at each time point was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale.

**FIGURE 3. Time to Relapse for Responders at Day 7 Among Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]**




[a] Response was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale (MADRS). Relapse was defined as a MADRS score of 20 or higher maintained for two consecutive visits and meeting criteria for a major depressive episode for 1 week.




## Discussion and Conclusion

In the studies investigating the effects of Ketamine infusions on patients with TRD, data has demonstrated that Ketamine produces a rapid-onset antidepressant effect. Significant improvements in clinician-administered and patient-reported depression severity ratings 24 hours following each infusion were observed. However, statistically significant differences in MADRS scores between the Ketamine and Midazolam groups were not observed after 7 days. These findings support the belief that NMDA receptor antagonism may provide relief of depressive symptoms in patients with TRD, although effects may not be long- lasting (Murrough et al., 2013).

Ketamine may have a more promising role in the management of SI, as clinically significant differences between “Wish to Die” and “Wish to Live” were recorded placebo-controlled trials. Ketamine may be a revolutionary approach in the reduction in mortality and morbidity of TRD (Ballard et al., 2014).

The large, rapid antidepressant effect of Ketamine is particularly significant given the poor prognosis for symptomatic improvement with commercial pharmacologic treatments in TRD. The Ketamine group reported transient psychotropic and hemodynamic effects but no episodes of emergent psychosis or mania throughout the follow-up assessments. These findings suggest that a Ketamine infusion of 0.5 mg/kg administered over 40 minutes is safe in the short-term treatment of TRD patients. It must be recognized that beyond this series of six infusions, the safety and efficacy of Ketamine in treating depression is unclear, and abuse liability and other issues associated with Ketamine necessitate a vigilant approach to its usage for purposes beyond research.


**References:**

Aan het Rot, M., Collins, K. A., Murrough, J. W., Perez, A. M., Reich, D. L., Charney, D. S., & Mathew, S. J. (2010). Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression. *Biological Psychiatry*, *67*(2), 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038

Ballard, E. D., Ionescu, D. F., Vande Voort, J. L., Niciu, M. J., Richards, E. M., Luckenbaugh, D. A., Brutsché, N. E., Ameli, R., Furey, M. L., & Zarate, C. A. (2014). Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety. *Journal of Psychiatric Research*, *58*, 161-166. https://doi.org/10.1016/j.jpsychires.2014.07.027

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., Charney, D. S., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *American Journal of Psychiatry*, *170*(10), 1134-1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., aan het Rot, M., Collins, K. A., Mathew, S. J., Charney, D. S., & Iosifescu, D. V. (2013). Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression. *Biological Psychiatry*, *74*(4), 250–256. https://doi.org/10.1016/j.biopsych.2012.06.022

Vande Voort, J. L., Morgan, R. J., Kung, S., Rasmussen, K. G., Rico, J., Palmer, B. A., Schak, K. M., Tye, S. J., Ritter, M. J., Frye, M. A., & Bobo, W. V. (2016). Continuation phase intravenous ketamine in adults with treatment-resistant depression. *Journal of Affective Disorders*, *206*, 300-304. https://doi.org/10.1016/j.jad.2016.09.008

Schwartz, J., Murrough, J. W., & Iosifescu, D. V. (2016). Ketamine for treatment-resistant depression: Recent developments and clinical applications: Table 1. *Evidence Based Mental Health*, *19*(2), 35–38. https://doi.org/10.1136/eb-2016-102355

Wan, L. B., Levitch, C. F., Perez, A. M., Brallier, J. W., Iosifescu, D. V., Chang, L. C., Foulkes, A., Mathew, S. J., Charney, D. S., & Murrough, J. W. (2014). Ketamine Safety and Tolerability in Clinical Trials for Treatment-Resistant Depression. *The Journal of Clinical Psychiatry*, *76*(03), 247–252. https://doi.org/10.4088/jcp.13m08852