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Ketamine as a treatment modality for treatment-resistant depression

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Abstract

Many recent studies have demonstrated the ability of ketamine, an NMDA receptor antagonist, to produce antidepressant effects that may be effective in helping reduce treatment-resistant major depression. In particular, three double-blinded randomized control trials have been conducted to assess the viability and effectiveness of this medication for treatment. This systematic literature review will analyze these studies and determine if the overall research indicates that ketamine is useful in improving depression as measured by the Montgomery–Asberg Depression Rating Scale (MADRS)[1].

Objective: Assess the effectiveness of IV Ketamine in reducing treatment-resistant major depressive disorder as measured by the Montgomery–Asberg Depression Rating Scale (MADRS)[1].

Design: Systematic literature review of three randomized control trials

Methods: Searches were done in PubMed utilizing the terms ketamine, depression, treatment-resistant depression, MADRS, placebo, and Montgomery-Asberg. In PubMed the following limits and terms were used: published in the last 10 years, humans, randomized controlled trial, adults >19 years, and English.

Results: Search criteria found three randomized control trials (RCTs) that met the inclusion/exclusion criteria: Fava et al (2018)[2], Murrough et al (2013)[3], and Phillips et al (2019)[4]. Fifteen additional trials were excluded based on the following: trials using esketamine (2), ones analyzing confounding variables (6), using polypharmacy (1), non-applicable studies using search terms (4), or non-blinded (1), and duplicate results (1).

Conclusion: All studies found that ketamine infusions resulted in statistical improvement on the MADRS scale among the trials' 213 participants in total. Each of the three trials administered ketamine at subanesthetic doses, and they all demonstrated effectiveness. While each of the studies showed improvement over placebo, they also showed improvement when compared to midazolam, and short-acting benzodiazepine. While the improvements were all noted at the 24-hour mark after administration, further study is needed to determine long-term effectiveness and safety.

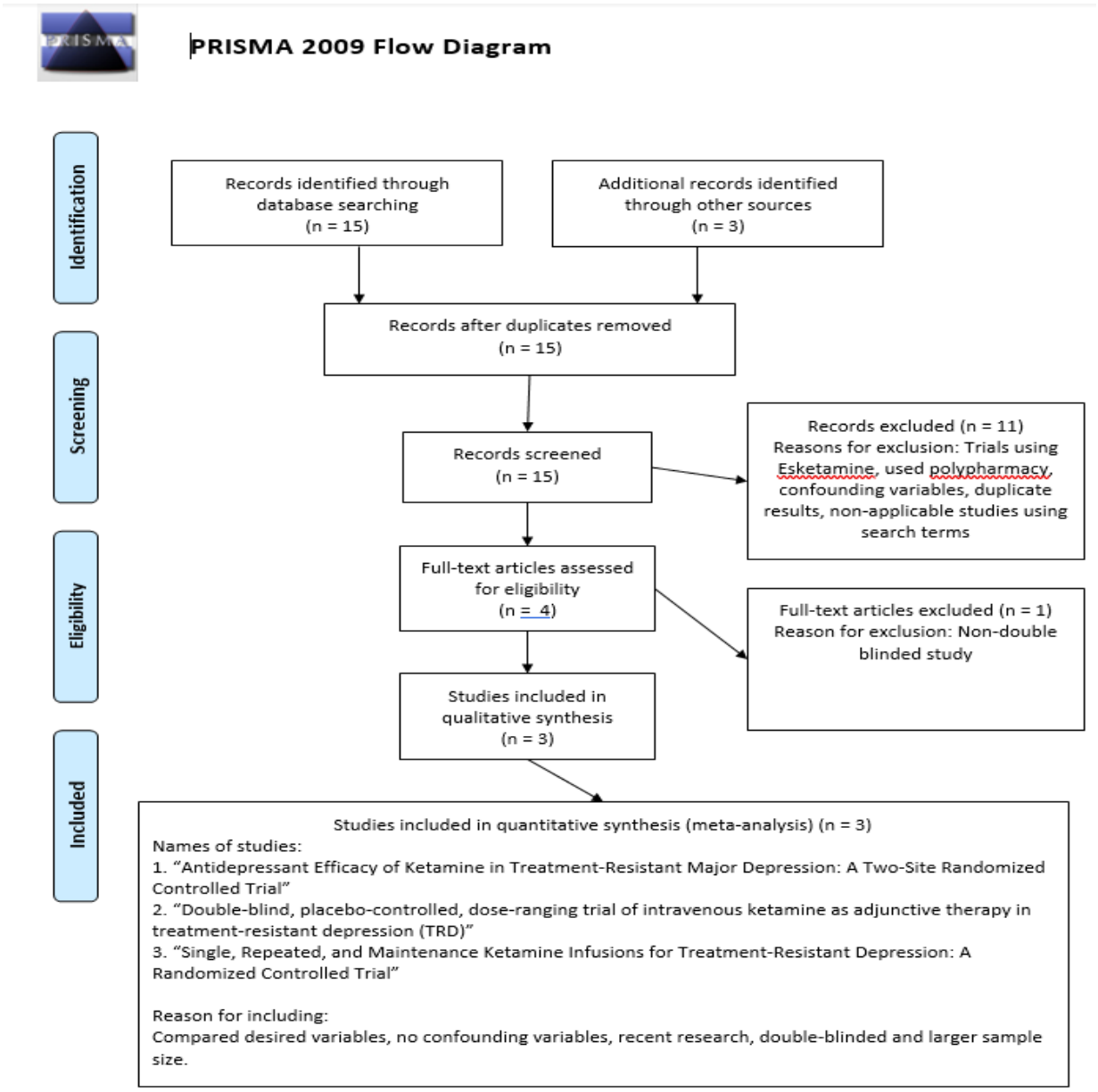
Introduction

In the United States, depression is a serious issue that affects a significant portion of the population. According to the National Institute of Mental Health, an estimated 17.3 million adults in the United States had at least one major depressive episode (7.1% of all U.S. adults in 2019)[5, 6]. 65% of these patients received treatment with medication as well as counseling. However, a significant portion of these patients still are unable to reach adequate response to these treatments. These patients are at high risk for many conditions. Not only do treatment-resistant states lead to higher rates of suicide, but they also increase risk of somatic complaints, heart disease, and obesity[7]. This can increase lifetime costs of care, as well as decreasing overall lifespan[7]. They are twice as likely to be hospitalized for depression. Patients with treatment-resistant depression have over 6 times the mean total medical costs of non-treatment-resistant depressed patients ($42,344 vs. $6512)[7].

Treatment-resistant depression (TRD) typically refers to inadequate response to at least one antidepressant trial, given standard doses and duration[8]. It is a relatively common occurrence, with 50-60% of the patients not achieving remission following antidepressant treatment. While there is not a standard definition of “adequate response”, measuring tools such as the Montgomery–Asberg Depression Rating Scale (MADRS) are used to monitor changes in patient mood and depression levels. The Montgomery–Asberg Depression Rating Scale (MADRS)[1] scores depression levels based on ten categories, with each category scored between 0-6. It was designed to more closely monitor the changes in mood with antidepressant treatment.

While there are many categories of antidepressant medications, ketamine provides a novel approach to treatment. As a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, it blocks HCN1 receptors. It also binds to the opioid mu and sigma receptors at higher dosage levels. While the exact mechanism of ketamine’s effects on depression is unknown, there are several prevailing theories. Some propose that ketamine reverses burst activity and theta-band synchronization in the lateral habenula. Others postulate that ketamine also may generate its antidepressant effects indirectly by blocking NMDA receptors on GABA interneurons.

This review aims to investigate IV ketamine as a safe and effective treatment for treatment-resistant depression. In particular, three double-blinded randomized control trials have been conducted to assess the viability and effectiveness of this medication for treatment. This systematic literature review will analyze these studies and determine if the overall research indicates that ketamine is useful in improving depression as measured by the Montgomery–Asberg Depression Rating Scale (MADRS).



PRISMA flow diagram: Searches were done in PubMed utilizing the terms ketamine, depression, treatment-resistant depression, MADRS, placebo, and Montgomery-Asberg.

Study Results

Study 1:

Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial [3]

Objective:

This study compares the usage of ketamine against placebo in the treatment of adults, looking at if ketamine is both efficient and rapid at producing depression remission.

Study design:

This study compared two different treatments (ketamine and midazolam). Midazolam was used as the placebo in this study. It was a two-site, parallel-arm, randomized controlled trial of a single infusion of ketamine. During a two-year period, patients deemed eligible for the study were screened and disqualified if they were outside of the age range (21-80), had comorbid psychiatric conditions such as bipolar, were taking contraindicated medications, or had a mini mental status exam of <27. Each patient had a physical examination, routine hematologic and biochemical tests, urine toxicology measurements, and an electrocardiogram (ECG) to screen out substance use or possible confounding medical conditions. In total, the study utilized 72 individuals.

This study randomly assigned patients (in a 2:1 ratio) to either a ketamine or a midazolam group. The patients received a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg) infused over 40 minutes. The drug vial was masked so that all were blinded to the treatment group until the point of analysis.

Patients were monitored from 240 minutes following the start of the infusion until discharge 24 hours after time of infusion. They then received outpatient evaluations 48 hours, 72 hours, and 7 days post infusion. Nonresponders were considered patients with less than 50% improvement from baseline (using the MADRS score). Nonresponders 7 days after the infusion were considered failures and not-followed further. Those who had a positive response were followed biweekly until relapse or for an additional 4 weeks, whichever came sooner.

Study Results:

Patients in the ketamine group had significantly greater improvement in the MADRS score at 24 hours than the midazolam group. After adjustment for baseline scores and site, the mean MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71), corresponding to a Cohen's d of 0.81. MADRS scores at 24 hours did not differ as a function of site ($F=0.63$, $df=1, 70$, $p=0.43$). The NNT was determined to be 2.8.

Both of the treatment groups demonstrated a small worsening in MADRS scores for every additional day postinfusion (95% CI, 0.00009 to 0.00062). Overall, patients in the ketamine group had lower MADRS scores (mean, 16.93; 95% CI, 14.03 to 19.82) than patients in the midazolam group (mean, 23.19; 95% CI, 19.03 to 27.34).

Study Critique

While this study used midazolam as a placebo due to the similar appearing effects on the patient, no true placebo was used. While it may be useful due to both the patient and provider seeing physical results of administration, it also adds confounding variables as midazolam may have some unexpected benefit. Adding a third inert group would have reduced this problem.

Study 2

Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression [2]

Objective:
The purpose of this study was to compare the effects of various dosages of ketamine against a midazolam placebo in improving short-term symptoms of depression.

Study Design:
This study was a double-blinded RCT. It was conducted across six US academic sites, and all patients were treated as outpatients. Participants were 18–70 years old with treatment resistant depression. 99 eligible subjects were randomly assigned to one of the five arms in a 1:1:1:1:1 fashion.

The categories included 4 groups who received various dosages of intravenous ketamine, as well as a single group who received midazolam at 0.045 mg/kg (n=19). The ketamine group dosages were as follows: 0.1 mg/kg (n = 18), 0.2 mg/kg (n = 20), 0.5mg/kg (n = 22), and 1.0 mg/kg (n = 20).

Each of the groups were screened with multiple depression rating scales ((HAM-D-6, MADRS, SDQ, PAS, CGI-S, and CGI-I) and were followed at 0, 1, 3 5, 7, 14, and 30 days to assess the safety and efficacy. For efficacy. Day 3 was determined to be the endpoint, but the patients were followed for an additional 30 days to determine benefit length.

Study Results:

On day 3, the MADRAS test was repeated. The results indicated a strong improvement for the 0.5 mg/kg ketamine group (p= 0.02, CI−16.56, −3.15). The primary screening tool, the HAM-D-6 assessment, showed 2 groups had statistically significant improvement on Day 1: the .5 mg/kg and the 1.0 mg/kg dose. The 0.5 mg/kg group had an adjusted p value of 0.00 (CI −7.35, −2.24), and the 1.0mg/kg ketamine group had an adjusted p value of 0.04 (CI −6.37, −1.15).

Only two of the other assessments besides the HAM-D-6 and the MADRAS showed statistically significant data. Statistical significance of the group × time interaction effect (considered their secondary outcome) was only achieved for the SDQ (p = 0.0105) and the PAS (p = 0.0341) in the 5-group comparison, and the PAS (p = 0.0332) and the CGI-S (p = 0.0204) in the 2-group comparison.

Additionally, side effects for all the groups given ketamine were higher. Headache (11.3% vs. 0%), nausea (10% vs. 0%), vomiting (5% vs. 0%), and depression (3.8% vs. 0%) were all higher in the ketamine groups vs the midazolam group. Additionally, 2 reported suicidal ideation in the

ketamine groups, while 0 did in the midazolam group. While overall the testing revealed depression improved, the self-reported increase in depression is important to note.

Study Critique:

One critique of this study is that they allowed patients to continue benzodiazepine usage if they were deemed stable on it for >4 weeks. This factor was not accounted for in the results, and a subgroup analysis would have been appropriate. Additionally, the MADRAS test was not administered on Day 1. As such, data was only listed for Day 3 for this group. While multiple measures were used, not all data from each group for each survey type was listed. This perhaps could indicate that the study only chose the survey types that showed a consistently positive result.

Secondly, at least four patients did not receive the dose indicated for their treatment group. Each of the four was underdosed, and each was due to an error in calculation. While each of these was reported, it may indicate a larger problem with the study.

Another possible confounding factor for the results was the ability of both clinicians and the participants to correctly guess if they had been given ketamine. For the two statistically significant groups (0.5 mg/kg and 1.0 mg/kg), both groups had extremely high correct guess (100% of clinicians and 77% for the 0.5mg/kg group, and 95% for both for the 1.0mg/kg group). This functional unblinding may have altered perceptions of improvement.

Additionally, this study did not publish the full results. Raw numbers are omitted and percentages used instead. P values are only given for some of the data. By omitting the raw data, it is impossible for full comparisons to be made.

Finally, there was some disparity in the groupings themselves. In the group where ketamine was administered at 0.2mg/kg, whites were the only racial group present. 98% of the women in the study were in just two groups: the midazolam group and the 1.0 mg/kg group. These disparities pose a problem, as the study was comparing the doses as well as the drug. As such, drastically different groups can pose a problem for application to wider populations.

Study 3:

Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial [1]

Objective:

This study evaluates the effects of a single ketamine infusion, a series of repeated ketamine infusions, and maintenance ketamine fusions.

Study Design:

This study was a double-blinded RCT that prescreened sixty-three individuals (age range of 18-65) for treatment-resistant depression by consultation with a study physician. They met the DSM-IV-TR criteria for major depressive disorder, single or recurrent episodes without psychotic features, confirmed with a mini-international neuropsychiatric interview. The inclusion criteria

was a score of 25 or more on the MADRS at screening and at randomization, with no more than 20% improvement between these visits. They also must have had at least psychotropic medication treatment for at least 6 weeks without any changes to their treatment during the trial. Exclusion criteria include a history of drug abuse or dependence, BMI of 35 or higher, history of mania or hypomania, and any unstable medical conditions.

Forty-six of the participants went through formal screening and forty-one participants went on to complete the study. The study was broken down into a three-phase clinical trial and positive response to ketamine was defined as a 50% or more decrease in MADRS from baseline (prior to start of phase 1).

In phase 1, the goal was to test the efficiency of ketamine compared to midazolam (the placebo, a short-acting benzodiazepine). Participants were randomly assigned in a 1:1 ratio to receive a dose of ketamine hydrochloride (0.5 mg/kg, diluted in 0.9% sale over a 40 minute IV pump) or midazolam (30 ug/kg, for 2 mg diluted in saline). The infusions were at least 7 days apart and they had to return to 80% of their baseline MADRS score before getting the other infusion, and phase 2. The medication bags were labeled drug A and drug B by an independent randomization. The study personnel and participants were debriefed after study completion.

In phase 2, the goal was to test the effects of repeat ketamine after relapse. The participants received six open-labeled ketamine infusions, administered three times a week, for 2 weeks. Participants who had at least a 50% improvement in MADRS score moved to phase 3. In phase 3, the goal was to observe the effects of maintenance ketamine when the frequency of infusions decrease from phase 2. The participants received ketamine infusions once weekly for four weeks. In both phase 2 and 3, the MADRS score was measured throughout the course of infusions. Follow up measures were obtained three days after the final infusion for each phase by study physicians.

Study results:

In phase 1, forty-one participants received the two infusions on an average of 10 days apart (range 7-36 days) and no difference in time gap between those who received one or the other drug first. The results show a significantly lowered MADRS total score after each ketamine infusion (mean decrease of 10.9 points) compared with midazolam infusion (mean decrease of 2.8 points), even after adjusting for baseline MADRS score, and order of drug administration. Twenty-four hours post ketamine infusion, 11 participants met antidepressant response criteria and 2 met remission criteria, but none met antidepressant response with midazolam in phase 1.

In phase 2, only thirty-nine completed from the forty-one participants. In the follow up visits, twenty-three participants met antidepressant response and 9 met remission. Responders had a mean decrease of 21.6 points in MADRS total score and nonresponders had a 3.1 point decrease.

In phase 3, 23 participants were included. All of the participants in this phase had at least a 50% improvement in their MADRS scores in the prior phase. Phase 3 was designated the maintenance phase. All participants were given once weekly ketamine doses, although no statistically significant improvement was noted in phase 3 ($p=0.49$). This indicates no further improvement after phase 2 levels.

Study critique:

The biggest critique of this study was that Phase 2 and 3 were open label, and thus lost the benefits of blinding on the data. While Phase 1 was double blinded, the lack of any blinding in the other phases may contribute to the assessment scoring.

A secondary limitation of this study was the fact that participants were continued on their current medication treatment throughout the study. The data did not separate these participants, so it is possible that the treatment is interacting in a way with the current medications that would be different from an otherwise unmedicated person. As such, the study results can only be read as ketamine being a useful adjunct, but not as primary treatment.

The study was fairly small, with only 41 participants (with only 23 continuing until phase 3). The small nature of this study impairs its ability for the results to be extrapolated to the larger population without additional studies.

Discussion

Major depression is a disease that affects millions in the United States alone. Current treatments have a poor success rate. Unsuccessfully treated depression leads to decreased overall health and risk of death to the patient, as well as costing the healthcare system millions of dollars. Ketamine, a medication often used for sedation and pain, has shown some promise in the treatment of depression. The purpose of this review is to determine whether ketamine, when compared against placebo, is effective at reducing treatment resistant depression.

An overview of the three studies is provided below (Table A). While each of the studies used the MADRS scale to determine the patient's subjective improvement at the 72-hour post administration mark, each of the papers had a slightly different focus. Murrough et al. followed the patients at the 1, 2, 3, and 7 day marks (with biweekly follow up until relapse or one month), and was focused on determining whether NMDA antagonists were likely to be effective as a treatment for depression. Maurizo et al. also compared the effectiveness of different dosages of ketamine, although it used the HAM-D-6 as the primary depression reporting tool, while only utilizing the MADRS on day 3 and not after 24 hours. Phillips et al. was unique in that it used multiple infusions over the course of the trial.

All three studies found significant improvement on the MADRS for ketamine (see table B), although Maurizo et al. found the significance only in the 0.5mg/kg and 1.0mg/kg ketamine dosages. This is notable for Murrough et al. and Phillips et al. also using the 0.5mg/kg dosage. As such, all three studies show significant improvement at the 0.5mg/kg dosage level, especially at the 24 hr mark (although Maurizo et al was using the HAM-6-D at that point). At the 72 hr common time mark, all three trials showed an improvement in scores utilizing the MADRS when comparing ketamine to placebo.

	Murrough et al	Phillips et al	Maurizo et al
Total	73	41	99

Patients, N			
Age Range	21-80	18-65	18-70
Study Type	Double blinded RCT	Double-blinded (phase 1 only) RCT	Double-blinded RCT
Intervention	Single Ketamine hydrochloride 0.5 mg/kg IV infusion	3 phases of Ketamine hydrochloride 0.5 mg/kg (0.9% saline) IV infusions	Single IV infusion of Ketamine 0.1 mg/kg, Ketamine 0.2 mg/kg, Ketamine 0.5 mg/kg, or Ketamine 1.0 mg/kg
Control	Single Midazolam 0.045 mg/kg IV infusion	SIngle Midazolam 0.03 mg/kg for 2mg (diluted in saline) IV infusion	Single Midazolam 0.045 mg/kg IV infusion
MADRS measurement time	24 hours postinfusion. Outpatient evaluation includes 48 hours, 72 hours, and 7 days postinfusion. Reponsders followed biweekly until relapse or for 4 more weeks, whichever earlier.	Phase 1: 2 hours, 24 hours, 7 days postinfusion Phase 2: Throughout the course of 6 infusions Phase 3: Throughout the course of 4 infusions	Day 3 after infusion.

Table A: Comparing the 3 studies reviewed in this article.

While each of the studies showed improvement at the 24 hour mark, it remains to be seen if the effect is lasting, or if (and how often) the treatment needs to be repeated. Murrough et al used a single dose to determine the effects through day 7. Maruizo et al followed up until day 30, where improvements against placebo were still evident. While the Phillips study had three phases that continued the timeline of monitoring longer, both of the later phases lost blinding, which reduces the applicability of comparison.

An important factor in whether ketamine treatment will be effective is the level of unwanted side effects. While the Phillips trial tracked and reported side effects using both the e Systematic Assessment for Treatment Emergent Events and the Clinician-Administered Dissociative States Scale, no serious adverse effects were noted. However, they did report side effects such as short-term elevation in blood pressure, cardiorespiratory effects, numbness or tingling, dissociation, dizziness, and visual disturbances. In the Maurizo study, headache, nausea, and vomiting were statistically higher effects than their midazolam placebo group. In that same study, there were also two more serious adverse events: one patient in the 0.2mg/kg ketamie group committed suicide during the trial, and another had abnormally high hepatic function

results. The Murrough study used the Patient Rated Inventory of Side Effects, the Clinician-Administered Dissociative States Scale, and the Brief Psychiatric Rating Scale positive symptom subscale, and found that blurred vision and poor concentration were more frequently reported in the ketamine group than the midazolam one. Of note, that study also found a correlation to increased blood pressure relating to higher doses of ketamine. These effects would have to be taken into account before treating patients, especially for longer term and at higher dosages.

	Patients, N	P value	Mean MADRS decrease	Response Rate (response + remission)	SD
Murrough et al Single Ketamine hydrochloride 0.5 mg/kg IV infusion	73	P<0.001	7.95	64%	NA
Phillips et al 3 phases of Ketamine hydrochloride 0.5 mg/kg (0.9% saline) IV infusions	Phase 1: 41 Phase 2: 39 Phase 3: 23	Phase 1: P<0.001 Phase 2: P<0.001 Phase 3: P=0.49	Phase 1: 10.9 Phase 2: 21.6 (responders), 3.1 (responders) Phase 3: 0	Phase 1: 31.71% (13/41) Phase 2: 82.05% (32/39) Phase 3: 91.30% (21/23)	Phase 1: 8.9 Phase 2: 5.8 (responders), 5.7 (nonresponders) Phase 3: 0
Maurizo et al Ketamine 0.1 mg/kg, Ketamine 0.2 mg/kg, Ketamine 0.5 mg/kg, Ketamine 1.0 mg/kg, or Midazolam 0.045 mg/kg	99 Ketamine 0.1 mg/kg: 18 Ketamine 0.2 mg/kg: 20 Ketamine 0.5 mg/kg: 22 Ketamine 1.0 mg/kg: 20 Midazolam	Ketamine 0.5mg/kg: Raw p: 0.00 Adj. p: 0.02	Ketamine 0.1 mg/kg: 33.8% Ketamine 0.2 mg/kg: 34.5% Ketamine 0.5 mg/kg: 31.6% Ketamine 1.0 mg/kg: 32.7% Midazolam	Ketamine 0.1 mg/kg: 31% Ketamine 0.2 mg/kg: 21% Ketamine 0.5 mg/kg: 59% Ketamine 1.0 mg/kg: 53% Midazolam	Ketamine 0.1 mg/kg: 5.9 Ketamine 0.2 mg/kg: 8.5 Ketamine 0.5 mg/kg: 3.9 Ketamine 1.0 mg/kg: 5.9 Midazolam 0.045

	0.045 mg/kg: 19		0.045 mg/kg: 33.6%	0.045 mg/kg: 33%	mg/kg: 7.1

Table B: Statistical breakdown of study data

Conclusion

In patients 18-65 years old with treatment-resistant depression, does ketamine reduce psychological distress compared to standard depression medication or placebo, as measured on the MADRS depression scale.

Intravenous ketamine, particularly at the 0.5mg/kg-1.0mg/kg dosages, is effective at improving feelings of depression in adult patients with a diagnosis of Major Depressive Disorder who are non-responsive to standard treatment. While short-term effectiveness and safety appear to be positive, more research is needed to determine long-term efficacy and need for repeat treatments.

References

1. Montgomery S, Åsberg M. A New Depression Scale Designed to be Sensitive to Change. British Journal of Psychiatry. 1979;134(4):382-389. doi:10.1192/bjp.134.4.382
2. Fava M, Freeman M, Flynn M et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2018;25(7):1592-1603. doi:10.1038/s41380-018-0256-5
3. Murrough J, Iosifescu D, Chang L et al. Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial. American Journal of Psychiatry. 2013;170(10):1134-1142. doi:10.1176/appi.ajp.2013.13030392
4. Phillips J, Norris S, Talbot J et al. Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial. American Journal of Psychiatry. 2019;176(5):401-409. doi:10.1176/appi.ajp.2018.18070834
5. NIMH » Major Depression. National Institute of Mental Health. https://www.nimh.nih.gov/health/statistics/major-depression.shtml#part_155033. Published 2020. Accessed October 5, 2020.
6. Center for Behavioral Health Statistics and Quality. (2018). 2017 National Survey on Drug Use and Health: Methodological summary and definitions. Rockville, MD: Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2017-methodological-summary-and-definitions
7. Crown W, Finkelstein S, Berndt E et al. The Impact of Treatment-Resistant Depression on Health Care Utilization and Costs. J Clin Psychiatry. 2002;63(11):963-971. doi:10.4088/jcp.v63n1102
8. Fava M, Davidson K. Definition and Epidemiology of Treatment-Resistant Depression. Psychiatric Clinics of North America. 1996;19(2):179-200. doi:10.1016/s0193-953x(05)70283-5