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Original Research Article

Efficacy of Ketamine in Antidepressants - Resistant Cases of MDD

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Abstract:

Introduction: Major Depressive Disorder (MDD) is characterized by enduring desolation, self-reproach, and cognitive haziness. Global prevalence ranges from 2% to 21%. Treatment involves pharmacological options like SSRIs, SNRIs, and atypical antipsychotics, as well as non-pharmacological approaches like cognitive behavioral therapy. Treatment-Resistant Depression (TRD) lacks a universal definition, posing challenges. Ketamine, once an anesthetic, now shows promise, rapidly alleviating symptoms through unique pharmacodynamics. This review aims to evaluate ketamine's efficacy and safety in treating MDD, especially in cases resistant to conventional therapies.

Methods: This research, conducted at our hospital from November 2022 to August 2023, investigates ketamine hydrochloride's effectiveness in treating major depressive disorder (MDD) for individuals resistant to three antidepressant treatments. The study includes participants aged 21–80 diagnosed with MDD. Exclusion criteria encompass psychotic or bipolar patients, recent substance misuse, unstable medical conditions, and others. The trial, involving 72 patients, uses statistical analyses to assess changes in depression severity and response rates. The research aims to comprehensively explore ketamine's antidepressant effects in treatment-resistant depression.

Result: In a study on treatment-resistant major depression, a single ketamine infusion demonstrated superior efficacy compared to midazolam. Ketamine users (n=40) exhibited a significant decrease in Montgomery-Åsberg Depression Rating Scale (MADRS) score (13.81) compared to the midazolam group (21.69). More ketamine patients showed a ≥50% MADRS score decline (47.5% vs. 20%) and were rated "much improved" or "very much improved" on the Clinical Global Impression Scale (35% vs. 15%) within 24 hours post-infusion. Adverse events varied, with ketamine users experiencing more nausea/vomiting and constipation. Blood pressure dynamics differed between groups, indicating potential implications for patient monitoring. The inpatient and outpatient ketamine groups exhibited greater and more sustained reductions in depression severity over 7 days compared to midazolam. Response rates favored ketamine at all time points, emphasizing its consistent and superior efficacy. Over 25 days, both drugs' efficacy declined, with ketamine showing a more rapid reduction. Alnefeesi et al.'s meta-analysis supports these findings, revealing substantial real-world efficacy of ketamine in treatment-resistant depression. Murrough et al.'s randomized controlled trial further underscores ketamine's rapid and significant antidepressant effects, emphasizing its potential as a novel intervention for severe and chronic depression.

Conclusion: This study concluded that people with severe depressive episodes that do not respond to therapy showed a rapid improvement in their depression symptoms after receiving a single infusion of ketamine.

Keywords: Major Depressive Disorder, Treatment-Resistant Depression, Ketamine, Antidepressant Effects, Efficacy.

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Introduction

Major Depressive Disorder (MDD) embodies a profound emotional landscape characterized by enduring feelings of desolation or melancholy, a dwindling attraction to once-enjoyable pursuits, persistent self-reproach, a sense of diminished vitality, cognitive haziness, shifts in appetite or sleep patterns, and at times, contemplations of self-harm. To merit an MDD diagnosis, an individual grapples with at least five of these indicators, including either a persistently despondent mood or a marked reduction in interest that significantly impairs social or occupational functions. Other facets within the realm of depressive disorders encompass an array of conditions such as persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, as well as those induced by substances or linked to medical

conditions, all shaping a multifaceted spectrum of depressive experiences [1,2].

The prevalence of Major Depressive Disorder (MDD) is a varied landscape, spanning global territories with distinct patterns. Across the world, the spectrum of lifetime MDD prevalence oscillates widely, encompassing figures ranging from 2% to 21%, notably exhibiting elevated rates in specific European regions while demonstrating relatively lower occurrences in certain Asian nations. In the United States, the temporal snapshot delineates a 12-month prevalence of 10.4% and a lifetime prevalence of 20.6% among the populace. Elderly demographics worldwide grapple with an MDD prevalence standing at 13.3%, while for adolescents, the point prevalence settles at 8%. Unveiling a glimpse into the medication-treated facet of MDD, the United States charts an estimated 12-month prevalence, with 8.9 million adults seeking pharmacological intervention for this condition [3-7].

The treatment landscape for Major Depressive Disorder (MDD) presents a diverse array of approaches, spanning both pharmacological and non-pharmacological realms. Pharmacological interventions encompass a spectrum of options, ranging from selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) to atypical antipsychotics like aripiprazole, brexpiprazole, cariprazine, extended-release quetiapine, and the olanzapine-fluoxetine combination. Augmentation strategies, involving lithium, liothyronine (T3), lamotrigine, or combinations of antidepressants like bupropion, tricyclics, or mirtazapine, have also proven effective. Among the cohort with treatment-resistant depression (TRD), ketamine and esketamine have emerged as promising therapies. Additionally, ongoing research explores novel avenues such as dual and triple monoamine uptake inhibitors, unconventional antidepressants like tianeptine, and agents interacting with endocannabinoid systems, neuropeptides, and growth and neurotrophic factors. On the non-pharmacological front, cognitive behavioral therapy (CBT) stands as a pivotal approach, reshaping thought patterns to influence moods and behaviors, offering a distinct alternative in managing MDD [8-10].

Treating Major Depressive Disorder (MDD) in individuals unresponsive to standard therapies, labeled as Treatment-Resistant Depression (TRD), poses multifaceted challenges. Foremost among these challenges is the absence of a universally agreed definition for TRD, complicating the establishment of a standardized treatment regimen. Switching or combining antidepressants, often attempted strategies, demonstrate limited efficacy in managing TRD. Additionally, while non-pharmacological interventions like psychotherapy, electroconvulsive therapy, and vagus nerve stimulation offer benefits, their widespread accessibility is constrained, and their positive effects may necessitate prolonged usage for noticeable outcomes. Moreover, the inherent diversity in depression's manifestations and underlying causes contributes to the complexity of evaluating and treating individuals resistant to conventional therapies, further complicating their care [9,11].

Ketamine, initially used as an anesthetic, has emerged as a beacon of hope in the treatment of severe and resistant depression. Its notable hallmark lies in its ability to swiftly induce powerful antidepressant effects, often within a matter of hours after administration. Notably, various studies underscore its capacity to significantly ameliorate symptoms associated with depression and anxiety. In particular, one study highlighted a remarkable outcome, noting that 20% of individuals grappling with treatment-resistant depression experienced a profound alleviation of their symptoms following biweekly ketamine injections over a month [12-14].

In 1962, ketamine was formulated with the aim of serving as a more manageable anesthetic than phencyclidine, featuring reduced hallucinogenic effects and a shorter duration of action. Its introduction to human use followed in 1964. However, as newer anesthetic agents emerged with improved side effect profiles, the utilization of ketamine as an anesthetic declined over time. Surprisingly, in recent decades, this N-Methyl-D-Aspartate (NMDA) receptor antagonist, ketamine, resurfaced as a ground breaking therapy for individuals grappling with treatment-resistant depression (TRD). What was once a sidelined anesthetic has now revealed unprecedented efficacy, swiftly and remarkably alleviating depressive symptoms within mere hours of administration, marking a pivotal turn in its medical application [12,15,16].

Ketamine, originally recognized for its anesthetic properties, has piqued interest due to its distinct pharmacodynamics, particularly in depression treatment. Its actions are believed to swiftly reverse synaptic stress pathology, activating postsynaptic glutamate to restore synaptic connectivity within a remarkably short span, possibly extending to days or even weeks after administration. The mechanism underpinning ketamine's effects revolves around antagonistic activity at the PCP site of the NMDA receptor complex, augmenting the activity of catecholamine and dopamine. Additionally, ketamine's impact on synaptic plasticity might involve a cascade of factors such as brain-derived neurotrophic factor (BDNF), eukaryotic elongation factor 2 (eEF2), mechanistic target of rapamycin (mTOR), and glycogen synthase kinase-3 (GSK-3). Its multifaceted mechanisms potentially encompass modulation of various systems, including AMPA

receptors, mTor signal pathways, monoaminergic systems, sigma-1 receptors, cholinergic, opioid, and cannabinoid systems. Moreover, it seems to interact with voltage-gated calcium channels and hyperpolarization cyclic nucleotide-gated channels. Of significant note isketamine's unparalleled speed in inducing antidepressant effects within hours, contrasting the delayed onset of traditional antidepressants that often require prolonged therapy for noticeable clinical responses [17-21].

The objective of this review or study is to assess the efficacy and safety of ketamine as a treatment for major depressive disorder (MDD), particularly in cases resistant to conventional therapies.

Method

Research Design

The research examined the effectiveness of ketamine hydrochloride in treating major depressive disorder (MDD) in individuals who had failed at least three antidepressant treatments. The enrollment period was from November 2022 to August 2023 at our hospital. Patients were to be 21 to 80 years old and diagnosed with major depressive disorder by the Structured Clinical Interview for DSM-IV. The Antidepressant Treatment History Form must also show that at least three antidepressant trials failed. A history of at least one major depressive episode or a particular Inventory of Depressive Symptomatology—Clinician-rated score was also required. A lifelong history of mental disease or bipolar disorder, recent alcohol or drug misuse, unstable medical conditions, substantial suicidal or homicidal risk, and medication contraindications excluded participants. Patient eligibility was determined by physical exams, laboratory testing, urine toxicological measures, and electrocardiograms. Participants gave informed permission after being fully informed about the research. Patients were randomized 2:1 to receive a single intravenous infusion of ketamine hydrochloride or midazolam, the latter acting as a control owing to its pharmacokinetic similarities. The trial needed patients to be off antidepressants and psychiatric medicines except for a steady nonbenzodiazepine hypnotic. All study staff were blinded to treatment allocation. In a clinical research facility, patients were monitored and rated for symptoms during and after the infusion. Depression severity decrease was the primary endpoint measured 24 hours post-infusion using the Montgomery-Åsberg Depression Rating Scale. Response rates, depressed symptomatology, Clinical Global Impression, and benefits up to 7 days post-infusion were secondary objectives. The research assessed adverse events, dissociative states, and psychotomimetic side effects using several measures. The research aims to investigate ketamine's antidepressant effects in treatment-resistant depression comprehensively.

Inclusion and Exclusion Criteria

Inclusion

- The age range for participants must be 21–80.
- Major depressive disorder must be the predominant diagnosis according to the Structured Clinical Interview for DSM-IV—Patient Edition.
- According to the Antidepressant Treatment History Form, eligible individuals must have failed at least three antidepressant therapy trials.

Exclusion

- Psychotic or bipolar patients with a lifelong history are excluded.
- Ineligible participants have abused alcohol or drugs within two years.
- Exclusion criteria include unstable medical conditions that might disrupt the investigation.

Statistical Analysis

The statistical power estimations used a 0.05 two-tailed alpha level. Previous research yielded effect size estimates of 0.71 for MADRS scores and 60% and 15% for ketamine and midazolam, according to Cohen's d. A 2:1 randomization of 72 patients (ketamine vs midazolam) was designed to identify changes in MADRS scores and response rates at 24 hours with 80% and 96% power. Statistical studies included all randomly assigned patients with baseline and at least one postbaseline assessment using modified intention-to-treat techniques. General linear models and logistic regression were used to analyze MADRS scores and response rates, adjusting for baseline and location. Secondary analyses employed descriptive statistics, general linear modeling, and ordinal logistic regression to quantify outcomes. A significance criterion of $p \leq 0.05$ was used for all statistical tests. Descriptive statistics examined safety and tolerability.

Result

Patients with treatment-resistant major depression (Ketamine n=40, Midazolam n=40) had similar demographic and clinical profiles. Both showed equal baseline depression severity, with similar mean scores on clinical measures such as the 30-item Inventory of Depressive Symptomatology—Clinician Rated, Montgomery-Åsberg Depression Rating Scale, and 16-item Quick Inventory—Self-Report. Although certain uncommon traits were observed, the groups' general well-matching supported comparing outcomes. The results provide a platform for future studies on Ketamine and

Midazolam infusions and treatment-resistant depression.

Table 1: Baseline characteristics of Patients with treatment-resistant major depression

Characteristic	Ketamine (n=40)	Midazolam (n=40)
Female sex	15 (37.5%)	17 (42.5%)
White	20 (50.00%)	21 (52.5%)
Hispanic ethnicity	22 (55.00%)	21 (52.5%)
Recurrent major depressive disorder	18 (45.00%)	17()
Chronic index episode (lasting ≥2 years)	15 (37.5%)	14 (42.5%)
Prior suicide attempt	13 (32.5%)	13 (32.5)
Prior psychiatric hospitalization	11 (27.5%)	12 (30.00%)
Melancholic features	8 (20.00%)	10 (25.00%)
Atypical features	12 (30.00%)	11 (27.5)
Unemployed	18 (45.00%)	17 (42.5%)
Married or cohabiting	19 (47.5%)	18 (45.00%)
	Mean + SD	Mean + SD
Number of major depressive episodes	11 (27.5%)	8 (20.00%)
Duration of index episode (months)	7 (17.5%)	6 (15.00%)
Previous antidepressant failures	6 (15.00%)	8 (20.00%)
Age (years)	9 (22.5%)	8 (20.00%)
Education (years)	10 (25.00%)	11 (27.5%)
Age at first major depressive episode (years)	13 (32.5%)	12 (30.00%)
Duration of major depressive disorder (years)	11 (27.5%)	10 (25.00%)
Body mass index (kg/m2)	15 (37.5%)	14 (35.00%)
Scores on clinical measures 30-item Inventory of Depressive Symptomatology—Clinician Ratedb	16 (40.00%)	13 (32.5%)
Montgomery-Åsberg Depression Rating Scalec	15 (37.5)	14 (35.00%)
16-item Quick Inventory of Depressive Sympto-matology—Self-Reportd	14 (35.00%)	13 (32..5%)

The 24-hour clinical state of treatment-resistant major depression patients following a single Ketamine or Midazolam infusion is shown in the table 2. Ketamine users showed better improvement on the Montgomery-Åsberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology—Self Report compared to the Midazolam group. A larger proportion of Ketamine patients had a ≥50% MADRS score decline, indicating a stronger therapy response. More Ketamine patients were rated "much improved" or "very much improved" on the Clinical Global Impression Scale than Midazolam within 24 hours after infusion, indicating better clinical results.

Table 2: Treatment-Resistant Major Depression Patients' 24-Hour Clinical Status After a Single Ketamine or Midazolama Infusion.

Clinical Measure	Ketamine (n=40)		Midazolam (n=40)	
	Mean	95% CI	Mean	95% CI
Montgomery-Åsberg Depression Rating Scale (MADRS) scoreb	13.81	10.69–16.79	21.69	19.01–26.60
Quick Inventory of Depressive Symptomatol-ogy—Self Report scorec	8.41	6.69–10.04	12.80	10.59–14.89
	N	%	N	%
Response: ≥50% decrease in MADRS scored	19	47.5	8	20
Clinical Global Impression Scale				
Improvement rating of 2 (much improved) or 1 (very much improved)e	14	35.00	6	15
Severity rating of 2 (minimally ill) or 1 (not at all ill)f	9	22.5	8	20

The table 3 shows side effects of a single Ketamine or Midazolam infusion in treatment-resistant major depressive patients. The two therapies have different adverse event frequencies. Ketamine users have greater nausea/vomiting and constipation. Both groups have dizziness and palpitations, but Midazolam worsens sensory symptoms including blurred vision and ringing in ears. These results emphasize the need of considering side effects when selecting Ketamine or Midazolam infusions for treatment-resistant depression, customizing therapy to patient tolerances and risks.

Table 3: Adverse Events in Treatment-Resistant Major Depression Patients Given a Single Ketamine or Midazolam Infusion

	New Onset or Worsening		**Distressing**		**New Onset or Worsening**		**Distressing**	
	Keta-mine	**Mid-azolam**	**Ket-a-mine**	**Mid-azo-lam**	**Keta-mine**	**Mid-azo-lam**	**Keta-mine**	**Mid-azolam**
Adverse Event a	N	%	N	%	N	%	N	%
Gastrointestinal								
Nausea/vomiti g	12	30.00	10		12	30.00	12	30.00
Dry mouth	8	20.00	12	30.00	12	30.00	12	30.00
Constipation	12	30.00	4	10.00	8	20.00	8	20.00
Diarrhea	8	20.00	4	10.00	5	12.5	5	12.5
Heart								
Dizziness on stand-ing	12	30.00	12	30.00	12	30.00	12	30.00
Palpitation	12	30.00	12	30.00	12	30.00	12	30.00
Chest pain	8	20.00	8	20.00	8	20.00	8	20.00
Skin								
Increased perspira-tion	12	30.00	12	30.00	5	12.5	12	30.00
Itching	5	12.5	12	30.00	12	30.00	12	30.00
Dry skin	7	17.5	8	20.00	12	30.00	8	20.00
Rash	4	10.00	6	15	8	20.00	7	17.5
Nervous system								
Dizzines	4	10.00	12	30.00	12	30.00	12	30.00
Headache	5	12.5	12	30.00	12	30.00	12	30.00
Poor coordination	7	17.5	8	20.00	8	20.00	8	20.00
Tremors	4	10.00	6	15	5	12.5	6	15
Eyes or ears								
Blurred vision	7	17.5	12	30.00	15	37.5	12	30.00
Ringing in ears	4	10.00	10	25	7	17.5	12	30.00
Genital/urinary								
Frequent urination	12	30.00	8	20.00	8	20.00	7	17.5
Adverse Event a								
Painful urination	12	30.00	12	30.00	12	30.00	12	30.00
Difficulty urinating	5	12.5	5	12.5	12	30.00	12	30.00
Other	7	17.5	7	17.5	8	20.00	8	20.00
Poor concentration	4	10.00	4	10.00	12	30.00	6	15
Restlessness	6	15.00	6	15.00	12	30.00	12	30.00
Anxiety	4	10.00	4	10.00	8	20.00	12	30.00
Decreased energy	5	12.5	12	30.00	12	30.00	8	20.00
Fatigue	7	17.5	5	12.5	12	30.00	6	15.00
General malaise	6	15.00	3	7.5	8	20.00	4	10.00

The table 4 shows treatment-resistant major depression patients' blood pressure (mm Hg) following a single Ketamine or Midazolam infusion. Both groups had similar baseline systolic and diastolic values. Ketamine increased systolic and diastolic pressures after 40 minutes after infusion compared to Midazolam. By 240 minutes post-infusion, Ketamine decreased systolic and diastolic pressures whereas Midazolam remained steady. Ketamine may cause a dynamic blood pressure response, which may affect patient monitoring during and after treatment.

Table 4: Blood Pressure of Treatment-Resistant Major Depression Patients After a Single Ketamine or Midazolam Infusion

Blood Pressure (mm Hg)								
Time	**Ketamine (N=40)**				**Midazolam (N=40)**			
	Systolic		**Diastolic**		**Systolic**		**Diastolic**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	119.6	14.8	71.7	11.3	119.8	14.5	69.3	10.1
40 minutes after infusion	139.5	15.4	79.8	13.5	109.5	15.3	70.2	10.1
240 minutes after infusion	131.3	15.4	69.5	7.8	109.8	12.9	69.5	6.9

Figure 1 shows the number of inpatients and outpatients getting ketamine or midazolam for depression over 7 days. The inpatient groups began with equal baseline values (ketamine: 30, midazolam: 32). Ketamine dropped to 18 and midazolam to 22 by Day 1. The outpatient ketamine group declined from Day 2 to Day 3 (17 and 16), then to Day 7 with 22 patients. However, midazolam outpatient values varied (22, 24) before settling at 20 on Day 7. This shows that ketamine may reduce depression severity more and longer over time.

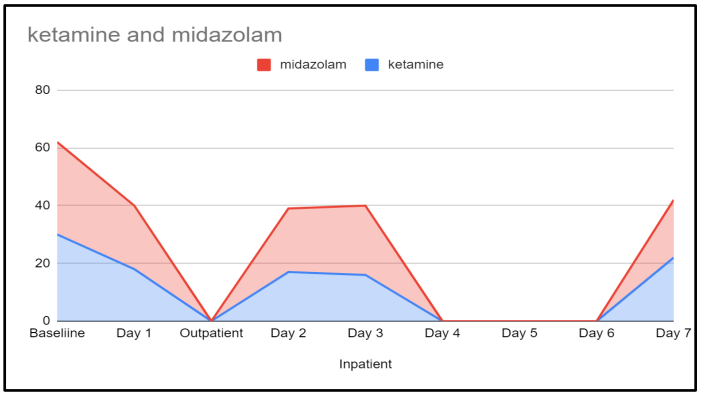

Figure 1: Change in Depression Severity Over Time in Patients

Treatment-resistant major depression patients receiving a single ketamine or midazolam infusion show response rates with time in Figure 2. Ketamine had a 50% response rate on Day 1 compared to midazolam's 20%. Day 2 and 3 showed similar trends (ketamine: 49%, midazolam: 22%). By Day 7, ketamine had a strong response rate (50%), whereas midazolam's climbed but remained lower (18%). A consistent and improved response to ketamine infusion compared to midazolam supports its potential use in treatment-resistant severe depression.

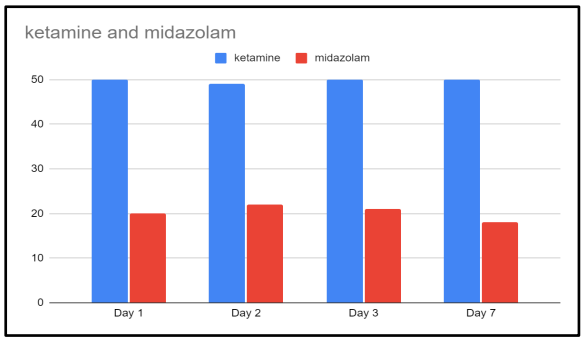

Figure 2: Over time response rates for treatment-resistant major depression patients given a single ketamine or midazolama infusion.

Ketamine and midazolam efficacy over 25 days is shown in Figure 3. Both drugs have Day 0 efficacy of 1. Later, ketamine's effectiveness drops to 0.15 by Day 25. Midazolam declines more steadily, reaching 0.2 by Day 25. Both medications lose efficacy with time, although ketamine loses more. This suggests monitoring the persistent therapeutic effects and tolerance development of ketamine and midazolam in a particular environment.

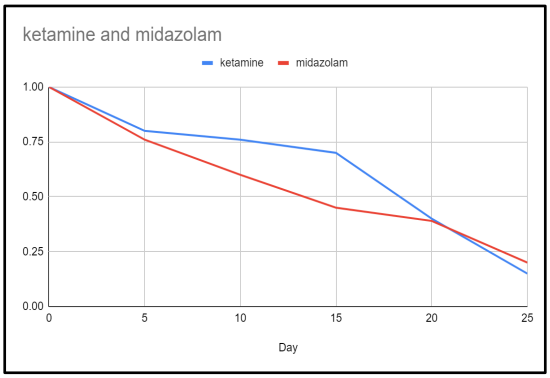

Figure 3: Response Time to Relapse at Day 7 for Patients with Treatment-Resistant Major Depression Receiving a Single Ketamine or Midazolama Infusion.

Discussion

Alnefeesi et al.'s (2022) expansive analysis delved into 79 studies encompassing 2665 patients, uncovering significant findings regarding ketamine's real-world efficacy in treatment-resistant depression (TRD). Their meta-analysis showcased substantial effects, with 45% of individuals responding, 30% achieving remission, and a Hedges g of symptom improvement at 1.44, emphasizing substantial relief among TRD patients. Notably, the study revealed varying response rates among individuals, highlighting the diverse outcomes. Resistant cases showed lower remission rates but not response rates, emphasizing the nuanced impact of ketamine. Intriguingly, repeated treatments did not notably diminish the therapeutic effect, suggesting sustained efficacy over time [22].

In a comprehensive study evaluating ketamine's rapid antidepressant efficacy, Murrough et al. (2013) conducted a randomized controlled trial involving 73 patients with treatment-resistant major depression. The trial compared a single infusion of ketamine to an active placebo control condition using the anesthetic midazolam. The results highlighted significant improvements in depression severity 24 hours post-treatment, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). The ketamine group displayed a notably greater reduction in MADRS scores compared to the midazolam group, showcasing an average difference of 7.95 points. Moreover, the likelihood of treatment response within 24 hours was substantially higher with ketamine, with response rates of 64% for ketamine versus 28% for midazolam. These findings underscore ketamine's rapid antidepressant effects, reinforcing its potential as a novel intervention for severe and chronic depression [23].

In an extensive exploration of ketamine's antidepressant effects beyond single infusions, a study by Murrough et al. (2013) encompassing 24 individuals with treatment-resistant major depression sought to unravel the pattern and endurance of ketamine's impact. The participants underwent a series of up to six intravenous ketamine infusions (.5 mg/kg) over 12 days. The study observed a remarkable overall response rate of 70.8%, showcasing a substantial mean reduction in Montgomery-Åsberg Depression Rating Scale

scores of 18.9 ± 6.6 at 2 hours post the initial ketamine infusion ($p < .001$). This reduction persisted consistently throughout the infusion period, portraying a sustained effect. Notably, responses at the 4-hour mark were highly indicative of study-end responses, being 94% sensitive and 71% specific in prediction. Among those who responded positively, the median time to relapse after the last ketamine infusion stood at 18 days. The study's findings underscored ketamine's swift and enduring antidepressant effect in treatment-resistant depression [24].

In a retrospective exploration by Vincenzo et al. (2021) aimed at discerning the comparative efficacy of ketamine treatment approaches for treatment-resistant depression (TRD), 220 patients' multidimensional self-reported outcomes were analyzed. The study juxtaposed monotherapy (n = 39) against adjunctive therapy (n = 181) involving ketamine at a community-based clinic. Both groups showcased clinically and statistically notable antidepressant effects ($p < 0.05$). Notably, those on ketamine monotherapy exhibited a significantly greater reduction in suicidal ideation (SI), as measured by the Quick Inventory for Depressive Symptomatology-Self Report 16-Item (QIDS-SR16) compared to the adjunctive group ($F (1, 265) = 4.73$; $p = 0.03$*; partial $\eta2 = 0.02$). Additionally, a higher proportion of partial responders was observed in the monotherapy group at post-infusion 4 ($p = 0.034$*). The study provides real-world evidence indicating the potential efficacy of ketamine as either monotherapy or adjunctive treatment in TRD [25].

In a study by Dwyer et al. (2021), 17 adolescents with major depressive disorder underwent a randomized, double-blind crossover trial comparing ketamine (0.5 mg/kg over 40 minutes) and midazolam (0.045 mg/kg over 40 minutes) as an active placebo. The primary outcome, the Montgomery-Åsberg Depression Rating Scale (MADRS) score at 24 hours post-infusion, exhibited a notable reduction in depressive symptoms with ketamine compared to midazolam (MADRS: midazolam mean=24.13, SD=12.08; ketamine mean=15.44, SD=10.07; mean difference=-8.69, SD=15.08; effect size=0.78). Secondary analysis highlighted that ketamine's benefits endured for 14 days post-treatment, as evidenced by MADRS scores, and a notably higher proportion experienced a response to ketamine within the initial three days compared to midazolam (76% and 35%, respectively). Ketamine's administration was generally well-tolerated, inducing transient dissociative symptoms without serious adverse events [26].

Ketamine, a promising treatment for treatment-resistant major depressive disorder (MDD), doesn't come without potential side effects. While common effects like headache, anxiety, dissociation, nausea, and dizziness are observed, serious adverse events like major dissociative episodes or auditory hallucinations are rare but possible. Some individuals may encounter less severe reactions such as skin rash, increased anxiety, headache, or exacerbated depression. However, transient dissociative symptoms often diminish with repeated dosing. Strategies aimed at alleviating these side effects involve adjustments in dosing and infusion rates, altering administration routes, or co-administering with mood stabilizers or antipsychotics. These approaches seek to balance the potential benefits of ketamine treatment with the management of its associated side effects [27,28].

Ketamine, known for its rapid antidepressant effects in individuals dealing with treatment-resistant depression (TRD), is generally deemed well-tolerated. However, it does come with some common side effects such as drowsiness, dizziness, coordination issues, blurred vision, and a sense of feeling strange or unreal. Among its potential adverse effects, transient increases in dissociative symptoms have been observed. In comparison to conventional antidepressants that might take several weeks to demonstrate efficacy and might not be universally effective, ketamine offers a contrasting timeline for potentially alleviating symptoms associated with TRD [29,30].

Ketamine's potential in managing Major Depressive Disorder (MDD), notably in treatment-resistant cases, holds promise, yet it confronts several hurdles and limitations. Concerns revolve around potential cognitive decline and psychomimetic effects, adding complexities to its usage. The absence of extensive long-term efficacy data poses a challenge, amplifying uncertainties about its sustained benefits. Questions linger regarding its safety profile and tolerability, further compounded by ongoing investigations into the optimal dosage and administration methods. Amid its potential, the necessity for extensive large-scale, randomized controlled trials remains paramount to authenticate both the effectiveness and safety of ketamine as a viable treatment for MDD [31-36].

Ketamine, a noncompetitive antagonist acting on NMDA receptors, presents a promising avenue in addressing treatment-resistant depression (TRD). Its rapid antidepressant effects, showcasing substantial alleviation of depressive symptoms within hours post-administration, have garnered attention in recent studies. However, uncertainties loom over crucial factors like the most effective dosage, administration frequency, and its enduring efficacy in the long term. Notably, ketamine exhibits promise in reducing suicidality within TRD populations. Yet, its usage isn't without drawbacks, with reported side effects encompassing confusion, emotional numbness, headaches, dizziness, and vision

disturbances. The quest for comprehensive insight continues, highlighting the need for further investigation to elucidate ketamine's prolonged efficacy specifically for individuals grappling with TRD [37-39].

Conclusion

This study concluded that people with severe depressive episodes that do not respond to therapy showed a rapid improvement in their depression symptoms after receiving a single infusion of ketamine. This research, which is the most extensive examination of ketamine in the treatment of serious depression that is resistant to other treatments, used a specially designed placebo that was intended to have similar effects to ketamine. The study provided new evidence that ketamine has specific antidepressant effects that are different from its general anesthetic features. Further studies should investigate the effectiveness of ketamine as an antidepressant beyond just one dose and examine its safety over a longer period of time to get a more complete knowledge of its potential as a therapy for serious depression.Despite the promising results of ketamine in treatment-resistant major depression, the research gap lies in the need for long-term studies assessing sustained efficacy and potential adverse effects over extended periods. Additionally, there is a lack of standardized criteria for defining and identifying treatment-resistant depression, posing challenges in comparing and generalizing findings across studies. Future research should focus on refining diagnostic criteria, conducting larger-scale trials with diverse populations, and exploring optimized administration protocols for ketamine. Addressing these gaps will contribute to a more comprehensive understanding of ketamine's role and guide its integration into clinical practice for antidepressant-resistant cases of Major Depressive Disorder.

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