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Long-Term Effects of Single and Repeated Ketamine Infusions on Treatment-Resistant Depression: A Retrospective Chart Review Study

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Abstract: Treatment-resistant depression (TRD) is a substantial public health burden with limited treatment options. Recent evidence suggests that single and repeated-dose ketamine infusions have rapid and significant antidepressant effects on individuals with TRD. Few studies have compared single or repeated (6) ketamine infusions past 14 days post-treatment. This retrospective chart review study investigated the long-term effects of single (n = 9) and repeated (6) (n = 5) high-dose (1 mg/kg) intravenous ketamine infusions on TRD 30 days post-infusion(s) (N = 14). Changes in depressive symptoms were measured by comparing Beck Depression Inventory (BDI-II) scores pre- and 30 days post-treatment for an understanding of long-term efficacy in clinical practice. Results indicated that ketamine has the potential to be an effective and enduring intervention for TRD, adding treatment and management options that are currently limited.

Keywords: treatment-resistant depression; ketamine; infusion therapy; beck depression inventory

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1. Introduction

Major depressive disorder (MDD) is a considerable public health concern and is the leading cause of mental health disability and impairment globally [1]. Current antidepressant treatments have low treatment adherence and efficacy due to negative side effects, slow treatment course, dependency concerns, or general ineffectiveness [2]. Current treatment approaches for MDD are typically pharmacological, psychotherapeutic, somatic, and combined. Pharmacological interventions include medications like selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants; all of which generally have low adherence rates and treatment outcomes [3]. Although these approaches work for some patients, there is a large population that continues to struggle with MDD symptoms even with modern treatment interventions.

MDD affects tens of millions of individuals every year and one-third of those affected continue to suffer from depression or become resistant to conventional pharmacologic, psychologic, or somatic treatments [4]. Of individuals with MDD, only 60–70% respond to antidepressant medications, and 10–20% of those who do not respond have treatment-resistant symptoms [5]. These individuals generally feel hopeless, with contemporary medical interventions unsuccessful in treating their debilitating symptoms, leading to greater socio-occupational impairment and a dramatic decline in physical health.

1.1. Treatment-Resistant Depression

Treatment-resistant depression (TRD) is defined as occurring when patients fail to respond to at least two different pharmacological classes of antidepressant medications, at adequate dosages, for at least 6 weeks, or failure to respond to previously effective

treatments in a succeeding depressive episode [6–8]. Up to 30% of individuals who have been treated for MDD are treatment-resistant [5,8]. This creates an even more exaggerated, debilitating disorder requiring research into novel and successful treatment interventions for TRD.

The biological mechanisms underlying MDD and TRD are poorly understood. Current antidepressant treatments require long-term courses to establish clinical responses, and a significant proportion of individuals are refractory to single-drug or combination treatments. These obstacles and more recent findings implicating synaptic plasticity involvement in the pathophysiology mechanisms of MDD are providing evidence for researchers to explore molecular mechanisms associated with this disorder and the development of subsequent treatments [9].

1.2. Ketamine

Ketamine is a dissociative anesthetic substance that has limited hallucinogenic effects [10]. It has recently been popularized as a psychedelic substance due to the altered state of consciousness it produces; however, the mechanisms of action are vastly different. Recently, ketamine has been one of the most studied potential antidepressant substances because of its rapid and significant therapeutic antidepressant effects in individuals with MDD and TRD [11]. Ketamine contains a chiral center, which allows it to have two enantiomers, R(−) and S(+) (esketamine), that are both used therapeutically [12].

1.3. History of Ketamine

In 1999, Ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act [10]. It is currently approved for medical use for short-term sedation and anesthesia for animals and humans, particularly in pediatric surgery because it does not suppress respiration [10]. In 2019, esketamine was approved by the FDA for nasal spray use for TRD, demonstrating a significant shift in drug policy regarding the medicalization of altered states of consciousness for therapeutic benefits [12]. Currently, ketamine is used 'off-label' for other psychiatric and pain disorders [13].

1.4. Ketamine Safety and Tolerability

Ketamine produces an altered state of consciousness, which can catalyze therapeutic change; however, it has the possibility of producing negative side effects and should only be used therapeutically under medical supervision. Negative side effects can include changes in blood pressure and heart rate, nausea, vomiting, sedation, and severe dissociation [14]. Ketamine can also lead to addiction or psychological dependence, through repeated use, with the possibility of detrimental cognitive impacts like dissociation and deficits in executive functioning such as memory or cognition [4,15]. Though ketamine can potentially produce negative side effects and detrimental effects through long-term use, under medical supervision and in the context of a clinical intervention, it can have therapeutic potential to manage depressive symptoms [16].

1.5. Ketamine Mechanism of Action

Ketamine has a unique mechanism of action and acts primarily as a N-methyl-D-aspartate (NMDA) receptor antagonist that produces glutamate modulation via NMDA and AMPA receptor actions [14,17–19]. Various downstream mechanisms occur through this process including the activation of brain-derived neurotrophic factor (BDNF) and mechanistic target of capamycin (mTOR) [9]. These signaling pathways are implicated in various complex cascade effects, notably neurogenesis and the potentiation of synaptic and neuronal plasticity [9,11,12,14,20]. Furthermore, ketamine produces widespread brain activation, which may disrupt faulty brain networks, and has been demonstrated through neuroimaging [4].

Ketamine blocks the NMDA receptor and inhibits calcium influx, leading to the release of GABA inhibition [4]. This causes a glutamate surge and a suppression of protein transla-

tion, leading to increased BDNF translation, enhanced neuroplasticity and synaptic growth, which are involved in the resolution of depressive symptoms [4]. As ketamine's mechanism of action is further studied, it is catalyzing research exploration into the biological mechanisms of MDD and its antidepressant effects for TRD.

1.6. Ketamine Antidepressant Effects

Ketamine is a unique substance because it has demonstrated rapid neuroprotective and antidepressant properties for MDD and TRD [14,15]. Traditionally, research has demonstrated that the pathophysiology of depression relies mainly on monoamine deficiency; however, modern animal and human research has pointed to glutamate NMDA receptors as being at the center of the pathophysiology of depression [14]. In this framework, ketamine, the non-competitive voltage-dependent NMDA receptor antagonist works through its distinct and rapid action on these receptors [14].

Furthermore, research on individuals with MDD and animal models has shown excitatory and inhibitory abnormalities in neurotransmission and neuronal plasticity, which may lead to deviant functional connectivity patterns within brain networks associated with altered brain levels of GABA and glutamate [14,18,21]. The combination of these findings suggests that the antidepressant effects of ketamine are associated with the specific mechanism of action through the reversal of neurochemical and physiological disturbances; along with the ability to reverse stress-induced neuronal changes and promote growth of new synaptic connections [15,21].

Additionally, research data provide evidence that ketamine's rapid and robust antidepressant effects may be due to its common dissociative effects, especially for specific depression subtypes [22–25]. The dissociative effects of ketamine may result from glutamate release enhancement, with individuals who experience more dissociation potentially having greater presynaptic glutamate release in response to the ketamine dose [26]. Various studies evaluating the relationship between ketamine's antidepressant effects and dissociative experiences in ketamine treatment for depression, bipolar disorders, and TRD have found significant correlations and associations between ketamine-induced dissociative symptoms and its antidepressant effects [22,23].

Dissociative experiences may be crucial to the antidepressant effects specifically in the depersonalized depression subtype because of ketamine's dissociative effects of disembodiment, which may suspend learned patterns of perceiving, behaving, and feeling through psychological plasticity and enhanced sensitivity [25]. Findings suggest that specific dissociative features may be strongly associated with antidepressant responses, though some studies have found no significant association between ketamine-induced dissociation and antidepressant effects [24,27,28].

1.7. Ketamine Therapy for Treatment-Resistant Depression

Ketamine's mechanism of action seems to alleviate depressive symptoms that other antidepressants do not target, making it a unique substance with which to treat TRD. Various studies have shown that a single, low-dose (0.5 mg/kg) ketamine infusion can rapidly alleviate depressive symptoms and suicidality in patients with TRD [29–32]. The rapid and significant antidepressant effects of subanesthetic levels of ketamine have been robustly confirmed in animal models and in individuals with TRD [9,29–35].

Findings from other experiments show enduring (14 days post-infusion) and significant antidepressant effects in MDD and TRD after repeated ketamine infusions, with the typical course being six ketamine infusions within 2–3 weeks [29,30,32–35]. The rapidly occurring antidepressant effects of ketamine infusions have been demonstrated in TRD; however, a gap in the literature exists relating to its enduring effects. The effects of single and repeated (6) high-dose (1 mg/kg) ketamine infusions on TRD have not been compared past 14 days post-infusion(s), indicating a need for the long-term antidepressant effects to be studied [36].

The current study addresses this gap by studying the longer-term effects on TRD of single and repeated (6) high-dose (1 mg/kg) ketamine infusions at 30 days post-infusion(s).

2. Materials and Methods

2.1. Participants

Patient charts from the private psychiatric practice of individuals with TRD who received the relevant treatment protocols between a two-year period of 2021 and 2023: one ketamine infusion group (n = 9) and repeated (6) ketamine infusion group (n = 5) were selected for review during a two-week chart review period. All patients had weekly psychotherapy with the same practitioner prior, during, and a minimum of 30 days post-infusion(s) at the private psychiatric practice where the chart review was conducted.

2.2. Measures

2.2.1. Beck Depression Inventory

The Beck Depression Inventory, second edition (BDI-II) is a 21-item self-report inventory that measures depression severity in adults and adolescents [37]. Each item is rated on a 4-point scale from 0 to 3, with the summation of scores ranging from 0 to 63. Summed scores fall into depression categories ranging from mild (14 to 19 points) to severe (29 points or more) depression. The BDI-II is a reliable and valid screening tool for depression widely used in clinical practice and research [38].

2.2.2. Antidepressant Treatment History Form

Treatment-resistant depression was defined as the failure to respond to at least two different pharmacological classes of antidepressant medications, at adequate dosages for at least 6 weeks during a depressive episode, or failure to respond to previously effective treatments in a succeeding depressive episode [6–8].

TRD was verified in the patient chart using the Antidepressant Treatment History Form (ATHF) which is a formalized method of evaluating treatment adequacy and resistance involving checking off each pharmacological class of antidepressant, brand of drug, length of treatment; along with other treatment modalities like psychotherapy [39].

2.2.3. Inclusion Criteria

Patient charts were reviewed to ensure all met the DSM-5 criteria for MDD, single or recurrent episode, as deemed by the physician who completed a structured clinical interview [40]. In addition, all baseline BDI-II scores were $\geq$14, indicating the presence of at least mild depressive symptoms. Further, the ATHF was used to verify that all patients included in the study had TRD. Finally, all were in regular, weekly psychotherapy with the same practitioner.

2.2.4. Exclusion Criterion

Patients who received ketamine infusion therapy in the last 30 days were not included to minimize any confounding variables.

2.3. Study Design

The study was a retrospective chart review of patients who met the criteria for TRD and completed the relevant treatment protocols, either single or repeated (6) ketamine infusion(s) with weekly psychotherapy, to investigate the long-term effects of ketamine infusion(s) on TRD 30 days post-infusion(s). All patients deemed fit for ketamine infusion therapy by the physician were prescribed the repeated (6) ketamine infusions; however, due to reasons other than clinical, like time and cost commitments, some patients elected for the single ketamine infusion. During the treatment, patients received subanesthetic high dose (1 mg/kg) compounded intravenous ketamine [31]. The repeated ketamine infusions were conducted within 2–3 weeks for maximum therapeutic benefit. As part of the standard protocol at the practice for these treatments, the patients completed a BDI-II two days pre-infusion and 30 days post-infusion(s), which were the data points used for the analyses of depressive symptom reduction. Data were analyzed using the Jamovi Statistics for MacOS (Version 2.3.19). A paired t-test was applied to compare changes in BDI-II scores at baseline (two days pre-infusion) and 30 days post-infusion(s) for the single and repeated

(6) ketamine infusion groups. The study was approved by the Institutional Review Board of the New School for Social Research BRANY (IRB Approval #24-132-1244).

3. Results

3.1. Clinical Characteristics

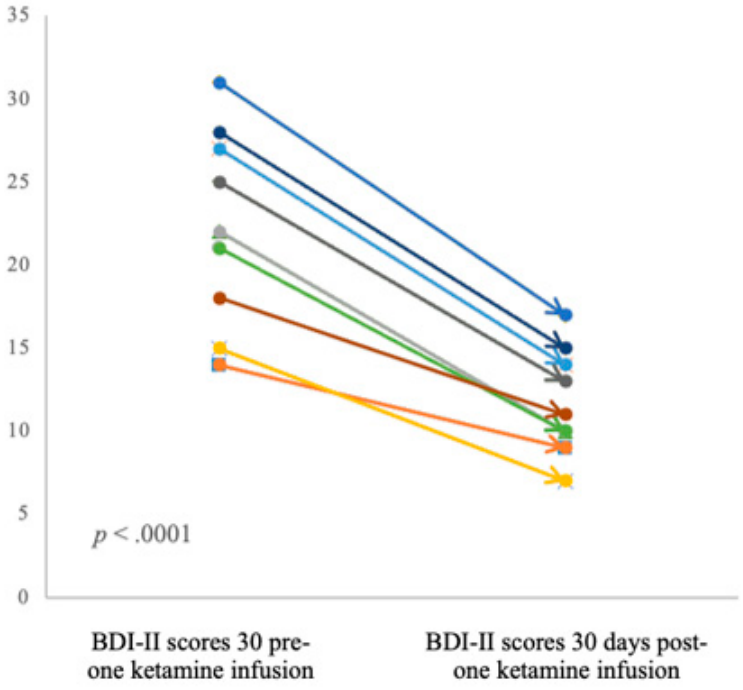
Table 1a,b show the descriptive statistics of the clinical characteristics of the patients. In the single infusion group, ages ranged from 22 to 66 years old (M = 44.1, SD = 11.4) and in the repeated (6) infusions group, ages ranged from 19 to 66 years old (M = 36.4, SD = 18.8). In the single infusion group, the majority were female (77%) and were recreationally drug-naive (88%); whereas in the repeated (6) infusion group, the majority were male (60%) and were recreationally drug-naive (60%). The severity of pre-treatment depression, as indicated by their baseline BDI-II score, varied in the single infusion group, with the majority being moderate depression (55%), then mild depression (33%) and one severe depression (11%). In the repeated (6) infusion group, all had severe depression pre-treatment (100%). None of the individuals had a history of substance abuse or substance use disorder. In the single infusion group, one individual had Bipolar II and in the repeated (6) infusion group, two individuals had depression with psychotic features.

Table 1. (a) Descriptive statistics of the clinical characteristics of patients in one infusion group (n = 9); (b) Descriptive statistics of the clinical characteristics of patients in repeated (6) infusion group (n = 5).

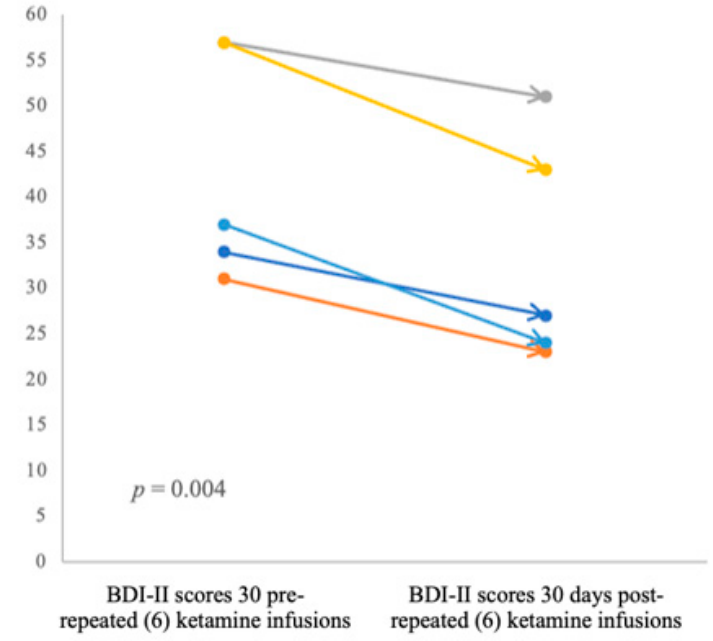
(a)	
Age of patient (years)	Mean ± SD M = 44.1 ± 11.4
Gender Male Female	Frequency (Percentage) 2/9 (22%) 7/9 (77%)
Diagnosis pre-treatment Mild depression Moderate depression Severe depression	Frequency (Percentage) 3/9 (33%) 5/9 (55%) 1/9 (11%)
Treatment history Recreationally drug-naive Antidepressants Mood stabilizers Antipsychotics	Frequency (Percentage) 8/9 (88%) 9/9 (100%) 2/9 (22%) 0/9 (0%)
Comorbidities Substance use disorder Bipolar II Psychotic features	Frequency (Percentage) 0/9 (0%) 1/9 (11%) 0/9 (0%)
SD = Standard deviation	
(b)	
Age of patient (years)	Mean ± SD M = 36.4 ± 18.8
Gender Male Female	Frequency (Percentage) 3/5 (60%) 2/5 (40%)
Diagnosis pre-treatment Mild depression Moderate depression Severe depression	Frequency (Percentage) 0/5 (0%) 0/5 (0%) 5/5 (100%)
Treatment history Recreationally drug-naive Antidepressants Mood stabilizers Antipsychotics	Frequency (Percentage) 3/5 (60%) 5/5 (100%) 2/5 (40%) 2/5 (40%)
Comorbidities Substance use disorder Bipolar II Psychotic features	Frequency (Percentage) 0/5 (0%) 0/5 (0%) 2/5 (40%)
SD = Standard deviation	

3.2. Long-Term Effects of Ketamine Infusion(s) on TRD

There was a significant reduction in BDI-II scores from baseline (M = 22.20, SD = 5.80) to 30 days post-single ketamine infusion (M = 11.70, SD = 3.08; $t(8)$ = 10.13, $p < 0.0001$). There was also a significant reduction in BDI-II scores from baseline (M = 43.2, SD = 12.80) to 30 days post-repeated (6) ketamine infusions (M = 33.6, SD = 12.6; $t(4)$ = 5.89, p = 0.004). These results, in Figure 1a,b below, show that there was an enduring and significant improvement in depressive symptoms at 30 days for both single and repeated (6) ketamine infusion(s).



(**a**)



(**b**)

Figure 1. (**a**) BDI-II scores pre and post-one ketamine infusion (n = 9). (**b**) BDI-II scores pre and post-repeated (6) ketamine infusions (n = 5).

3.3. Depression Categorizations Pre- and Post-Infusion(s)

In the single infusion group, the majority of the participants' baseline depression categorizations, as indicated by their baseline BDI-II score, were mild or moderate depression, 33% and 55%, respectively. After the single ketamine infusion therapy intervention, the majority of the participants shifted to depression categorizations of clinically 'normal' and/or mild depression, 44% and 55%, respectively. In the repeated (6) infusions group, all of the participants were categorized as severely depressed at baseline (100%). After the repeated (6) infusions, the majority of the participants (60%) shifted to a depression categorization of 'moderate' depression. In addition, although their BDI-II scores did decrease, the two participants' scores remained in the severe range (40%). Table 2a,b show the changes in BDI-II categorizations of depression from pre and post-infusion(s) for each individual in the single and repeated (6) groups, respectively. Though the baseline depression scores were different between the two groups, it is important to note that every participant improved; 100% had a lower BDI-II score 30 days post-infusion(s) than their baseline BDI-II score, suggesting that ketamine infusion therapy has powerful antidepressant effects and is an effective therapeutic intervention.

Table 2. (a) Changes in BDI-II scores of patients in one infusion group, pre and post-infusion (n = 9); (b) Changes in BDI-II scores of patients in repeated (6) infusion group, pre and post-infusions (n = 5).

(a)	
Diagnosis pre-treatment	Frequency (Percentage)
Mild depression	3/9 (33%)
Moderate depression	5/9 (55%)
Severe depression	1/9 (11%)
Diagnosis post-treatment	Frequency (Percentage)
Clinically 'normal'	4/9 (44%)
Mild depression	5/9 (55%)
Moderate depression	0/9 (0%)
Severe depression	0/9 (0%)
(b)	
Diagnosis pre-treatment	Frequency (Percentage)
Mild depression	0/5 (0%)
Moderate depression	0/5 (0%)
Severe Depression	5/5 (100%)
Diagnosis post-treatment	Frequency (Percentage)
Clinically 'normal'	0/5 (0%)
Mild depression	0/5 (0%)
Moderate depression	3/5 (60%)
Severe depression	2/5 (40%)

4. Tolerability and Safety

No serious adverse events that led to discontinuation or safety issues were in the chart review. Mild nausea was reported in one case and treated with ondansetron post-infusion.

5. Discussion

With the debilitating nature of depression and TRD affecting millions globally, the need for effective treatment options is crucial [1,14,41]. The significant and rapid antidepressant effects of subanesthetic levels of single and repeated ketamine infusion(s) have been robustly confirmed in animal models and in individuals with TRD [9,29–35]. The current study aimed at understanding the efficacy and endurance of ketamine's antidepressant effects for single and repeated (6) ketamine infusion(s) at 30 days post-infusion(s) in TRD. The findings of this retrospective chart review study suggest that a single high-dose (1 mg/kg) ketamine infusion and repeated (6) ketamine infusion(s) administered

within 2–3 weeks contribute to significant enduring decreases in depressive symptoms of individuals with TRD.

In alignment with the current findings, previous studies have shown that a single, low-dose (0.5 mg/kg) ketamine infusion can rapidly reduce depressive symptoms for about one week in individuals with TRD [29–32]. Research data from other studies demonstrate significant antidepressant effects in MDD and TRD after repeated ketamine infusions, with the typical course being six ketamine infusions within 2–3 weeks [29,30,32–35]. Some individuals experience a relapse in depressive symptoms following treatment, pointing to the possible need for repeated ketamine infusions to prolong the antidepressant effects, especially in more severe symptom presentations [16,29,33,35].

In a study aimed at evaluating the antidepressant effects of a single and repeated (0.5 mg/kg) ketamine infusion(s) for TRD, the authors found that repeated ketamine infusions have cumulative and sustained antidepressant effects, as measured by Montgomery–Asberg Depression Rating Scale (MADRS), at 7 days post-infusions, compared to a single ketamine infusion [30]. While results are encouraging, most individuals with TRD are seeking effective *and* enduring antidepressant treatment options. The current study's results demonstrate that both single and repeated (6) ketamine infusion(s) are clinically effective in the reduction and management of depressive symptoms in individuals diagnosed with TRD at 30 days post-infusion (s). Another study found that the antidepressant effects of repeated ketamine infusions were not significantly greater than the single infusion, as measured by MADRS at the end of treatment, and this study had a 6-month post-treatment time frame critical to understanding the enduring effects [32]. All participants improved in the current study (100%), as seen in a reduction in BDI-II scores 30 days post-infusion (s) from their baseline score, though the baseline scores between the two groups differed greatly, with the repeated (6) group having a more severe symptom presentation. The improvement of BDI-II scores for all of the individuals suggests that ketamine infusion therapy has the potential to be an effective therapeutic intervention for the management of TRD, even for more severe presentations.

As discussed previously, all participants were recommended for repeated (6) ketamine infusions; however, due to non-clinical reasons like cost or time commitments, some patients opted for the single ketamine infusion. Retrospectively, it is clear that participants self-selected their treatment based on their depression symptom severity. All of the participants in the repeated (6) infusion group had baseline depression in the severe range (Mean BDI = 43.20 $\pm$ 12.80), and potentially chose the more intensive treatment regardless of the cost or time commitments. The baseline BDI-II scores for the single infusion group were significantly lower (Mean BDI = 22.20 $\pm$ 5.80), indicating a less severe sample in the single infusion group than in the repeated (6) infusion group. However, both groups demonstrated significant decreases in BDI-II scores 30 days post-infusion, indicating that one and repeated (6) ketamine infusion(s) had enduring antidepressant effects for TRD, even in more clinically severe symptom presentations and diagnostic categorization.

Interestingly, most previous studies have utilized low-dose (0.5 mg/kg) intravenous ketamine to reduce and manage depressive symptoms in TRD; however, this study reviewed high-dose (1 mg/kg) intravenous ketamine treatments and found significant reductions in depressive symptoms in both single and repeated (6) infusion(s), regardless of baseline depression categorization. This may point to the need for high-dose ketamine infusion(s) to provide an enduring antidepressant effect. In a study designed to find the optimal dose range for single ketamine infusion in TRD, the authors found that the standard low dose (0.5 mg/kg) and high dose (1 mg/kg) were superior to the active placebo, suggesting that both low-dose (0.5 mg/kg) and high-dose (1 mg/kg) ketamine are clinically effective in the reduction in depressive symptoms [31]. As others have posited, repeated ketamine infusions have cumulative effects so perhaps doubling the low dose to a high dose has a cumulative effect, as well [30]. Additionally, following the idea that ketamine's antidepressant effects are due to its dissociative effects, higher doses of ketamine may

further enhance glutamate release and subsequent dissociative effects, producing a longer antidepressant effect [26].

Following ketamine infusions in this study, the majority of participants in the repeated (6) infusion group (60%) shifted from severe depression to moderate depression. This change highlights the tremendous clinical potential for both rapid and enduring treatment effects for severely depressed individuals with TRD. This is aligned with previous studies that have shown a reduction in severe depressive symptoms in TRD, specifically suicidal ideation and psychotic features [30,33,42]. Furthermore, the results from the single infusion group in this study demonstrate the clinical potential for moderate to mildly depressed individuals with TRD for a rapid and enduring intervention. Most of the participants' baseline depression scores indicated mild or moderate depression, 33% and 55%, respectively. After the single ketamine infusion therapy intervention, the majority of the participants shifted to a depression categorization of clinically 'normal' and mild depression, 44% and 55%, respectively.

This study was unique in that it controlled for psychotherapy during the ketamine therapy process, as all patients had weekly psychotherapy with the same practitioner prior, during, and a minimum of 30 days post-infusion(s). This may also provide insight into the enduring antidepressant effects sustained post-infusion(s). Ketamine is thought to moderate pathological belief structures related to depression, and together with psychotherapy and neuroplasticity, may allow for enhancement to the therapeutic process and sustained antidepressant effects [24,43].

The predominant implication of this study is that ketamine infusion therapy adds to therapeutic options for TRD, which have previously been extremely limited. It also provides an option for eradicating daily intake of medications with unwanted side effects and limited effects. Confirming that both one and repeated (6) ketamine infusion(s) have enduring antidepressant effects can save both patients and practitioners time and money by creating an experience-based therapeutic framework with lasting effects. Additionally, the ability of ketamine treatment to create clinically relevant changes in depression levels is a tremendous advancement in the field of psychedelic therapy that can be further explored as a catalyst for change. As many antidepressant medications do not work until several weeks after initiation, ketamine infusion therapy may be clinically indicated for patients who need a respite from the debilitating symptoms of depression or TRD.

5.1. Limitations

There are a few limitations to this study. This study was a retrospective and observational study, not a randomized double-blind comparison study with a placebo control which would have been optimal for demonstrating the therapeutic effects of ketamine therapy. The sample was a small convenience sample and only individuals with the means to pay out of pocket for psychiatric care were included. Furthermore, it was noted that patients with higher scores on the BDI-II self-selected the repeated (6) infusion group and there was a lack of homogeneity in the baseline BDI-II scores indicating severity. A future study would control for the level of depression as well as for treatment conditions.

5.2. Directions for Future Research

Psychotherapy in conjunction with ketamine infusion therapy has mixed results indicating its effectiveness. In this study, patient charts of individuals who received ketamine infusion therapy and weekly psychotherapy with the same practitioner prior, during, and a minimum of 30 days post-infusion(s) were analyzed for consistency. Focusing on the benefits of psychotherapy in conjunction with ketamine infusion therapy, or different routes of delivery of ketamine during psychotherapy, would add to the therapeutic framework and create more options for patients and practitioners. Ketamine can aid in the relaxation of beliefs related to pathological self-representational models, and in conjunction with neuroplasticity, psychotherapy may enhance the long-term antidepressant effects [24,43]. Maintenance infusions and psychotherapy, along with measuring antidepressant effects

at 60, 90, and 120 days post-infusion(s) would be the first study of its kind. Comparing ketamine infusion therapy with and without psychotherapy would represent an advancement in the study of mediating and modulating the effects of medication and therapy. Furthermore, adding a Clinician-Administered Dissociative States Scale (CADSS) scale to ketamine treatment protocols may be helpful in parsing out specific dissociative features that are linked to its antidepressant effects [23]. Exploring different ketamine doses may also be illuminating to see if the severity of baseline depression can be reduced with higher doses and if higher doses are linked to increased dissociative experiences and increased enduring antidepressant effects.

This study establishes the enduring antidepressant effects of single and repeated (6) high-dose (1 mg/kg) ketamine infusions for TRD at 30 days post-infusion(s), in the context of intravenous ketamine in conjunction with weekly psychotherapy. There are many areas for further research such as focusing on the biological mechanisms underlying MDD, TRD, and the ketamine mechanism of action to further elucidate pathophysiologies and remedies. Exploring comprehensive biological testing of markers like GABA, glutamate, mTOR, NMDR, and pre- and post-ketamine infusion would add to the literature to confirm effects including neurogenesis and synaptic plasticity. Combining these directions with neuroimaging during tasks and psychotherapy may be fruitful.

6. Conclusions

This study provides a foundation for further research relating to ketamine as a psychoactive substance to catalyze therapeutic change. The results of the present study suggest enduring antidepressant effects of single and repeated (6) high-dose (1 mg/kg) ketamine infusion(s) for individuals with TRD. The opportunity to help one-third of the MDD population is here and with more research, it seems there is a potential for the management of TRD.

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Informed Consent Statement: Informed consent was obtained from all participants in this study.

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