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**ORIGINAL ARTICLE**

# Exploring Ketamine's Expanding Roles Beyond Anesthesia, Including PTSD, Chronic Pain, and Depression Treatment

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## ABSTRACT

**Introduction**: Ketamine, traditionally known for its anesthetic properties, is now being explored for its rapid-acting therapeutic effects in various psychiatric and pain-related disorders. Its emerging role in managing treatment-resistant depression (TRD), chronic pain, and post-traumatic stress disorder (PTSD) is supported by recent clinical evidence.

**Objective**: To evaluate the effectiveness of ketamine in the treatment of chronic pain, TRD, and PTSD among patients in a tertiary care setting.

**Materials and Method**: This retrospective observational study was conducted at Anesthesia Department, Lady Reading Hospital-MTI Peshawar, Pakistan, from January, 2023 to June, 2023. Based on the predetermined inclusion and exclusion criteria, 70 records for patients receiving ketamine treatment were assessed. Clinical outcomes were assessed using standardized rating scales for pain, depression, and PTSD.

**Results**: Substantial healing occurred for each condition, and symptom severity was significantly reduced following ketamine treatment. Overall, 78.5% of patients had positive responses with no adverse effects.

**Conclusion**: Ketamine represents a viable and fast-acting alternative treatment for patients with refractory psychiatric conditions and pain.

**Keywords**: Ketamine, depression, PTSD, chronic pain, treatment-resistant, rapid-acting therapy, NMDA antagonist.

## INTRODUCTION

Ketamine was first synthesized in the late 1960s as a dissociative anesthetic. It has a long history of use as a medication (such as a general anesthetic) in various medical and surgical settings, paramedicine, and emergency medicine due to its fast onset of action, safety profile, and mechanism of action[1]. However, the past few decades have shifted the focus of ketamine from a medicine used primarily for surgical procedures to a drug of increasing interest in off-label uses, particularly chronic pain, post-traumatic stress disorder (PTSD), and treatment-resistant depression (TRD)[2]. While the shift in emphasis has occurred as a result of an evaluation of ketamine's mechanisms and its potential for therapeutic use based on extensive scientific studies of the drug, ketamine is an emerging agent of interest in both psychiatry and pain medicine[3]. The growth of interest in ketamine as an agent for chronic pain remains rooted in the unique aspects of ketamine as an N-methyl-D-aspartate (NMDA) receptor agonist by modulating both peripheral and central pain pathways. Research evidence indicates that ketamine decreases allodynia, hyperalgesia, and central sensitization, all of which relate to chronic pain syndromes[4].

Clinical evidence suggests ketamine infusions elicit analgesia lasting well beyond the plasma half-life, suggesting long-term neuroplastic changes in circuits that process pain[5]. Ketamine is now finding use for pain conditions, especially complex regional pain syndrome (CRPS), fibromyalgia, and cancer pain, typically for patients when standard pharmacotherapy has not helped. In addition to analgesia, ketamine has also become a hot topic due to its rapid-acting antidepressant properties in patients suffering from treatment-resistant depression (TRD). These patients have not seen any change with standard selective serotonin reuptake inhibitors (SSRIs) and other agents[6]. In contrast to standard antidepressants such as SSRIs, which take weeks to show any effect, ketamine is observed to improve mood in a few hours, utilizing the glutamatergic system and increasing synaptic plasticity[7].

This quick response is vital for patients experiencing acute psychological suffering, particularly those at increased risk of suicide[8]. This antidepressant inspired responses to ketamine improve even further when paired with psychotherapy and individualized, complete treatment plans, potentially designating the drug as a foundational aspect of integrative mental health treatment[9]. Ketamine might also have an equally significant role in the treatment of PTSD. Patients (and not only psychiatric patients) can exhibit abnormal fear extinction or excessive reactivity from the amygdala, both of which benefit from the neuropharmacology of ketamine[10]. Some research suggests that ketamine can interfere with the reconsolidation of trauma memory, assist in extinction learning, and enhance emotional flexibility, addressing the things that people with PTSD suffer from[11]. Additionally, neuroimaging studies showed that ketamine increases connectivity between the prefrontal cortex and limbic system, encouraging top-down regulation of emotional reactivity.

These results are remarkable and important, especially as existing pharmacotherapies for PTSD are not very effective and there is a critical need for new ones[12]. Ketamine is being used recreationally for these psychiatric domains, and it has also been studied for its use in the prevention of chronic postsurgical pain and preoperative mood aberrations. Ketamine targets the affective components of pain to help reduce physical pain and improve emotional pain[13]. This is highly useful in surgical populations where psychological burden may predispose patients to persistent pain syndromes that go unaddressed. Recent systematic reviews also suggest that ketamine has potential in substance use disorders and ketamine may increase motivation towards recovery and reduce cravings through processes, but likely through modulation of reward circuitry in the brain.

The molecular basis of ketamine's many therapeutic actions is remarkably complex and diverse. In addition to NMDA blockage, ketamine affects numerous other receptors and intracellular signaling pathways, including BDNF signaling, AMPA receptor activity, and mTOR signaling[14]. These pathways are assumed to underlie the pharmacological effects of ketamine, including its ability to promote synaptogenesis and ameliorate the neurotoxicity of stress in the brain related to mood and executive function. As research progresses, these findings provide the tools to make more targeted and refined formulations of ketamine, including its enantiomer (R)-(-)-ketamine, which seems to have an improved side-effect profile and better antidepressant activity[15]. Preclinical research has led to additional evidence for the effects of ketamine on fear extinction and memory reconsolidation, which are fundamental components for the treatment of trauma-related disorders.

The findings of these studies support the theory that ketamine may provide a synergistic effect, just like how it is presumed to have a synergistic effect in trauma-informed

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psychotherapy, as a therapeutic context[5,18]. Despite the fact that ketamine therapy offers promise, there are many challenges to face. Most importantly, the implications of ketamine as a substance with abuse potential, the implications of its dissociative side effects, and ensuring a sufficiently structured therapeutic environment[16] are all important clinical considerations that needs to be faced going forward. The creation of novel approaches to improve patient satisfaction and treatment outcomes, like using virtual reality along with a ketamine infusion process, is becoming more evidence-based on principles of immersive environments conducive to psychological healing. The potential of ketamine as a therapeutic drug was demonstrated in unconventional contexts, an example of this being in space missions where the use of ketamine to manage psychiatric emergencies was explored in an extreme, but also resource-limited context[17].

The military and prehospital care sectors have been no exception in using ketamine in consideration of its unique safety profile and analgesic effects in field conditions, further supporting evidence of ketamine's versatility[13]. As the therapeutic ecosystem continues to take shape, it is evident that ketamine is in a distinct space among psychiatry, neurology, and pain medicine. The future of ketamine-regimen-oriented treatment will likely include personalized, multidisciplinary approaches with a therapeutic course through pharmacological and psychotherapy aspects[18]. Ketamine's transition from anesthetic use to psychiatric and analgesic means is one of the most significant changes to occur in modern pharmacotherapy, and there remains much to learn moving forward as research continues to elucidate ketamine's mechanisms and support its clinical use more effectively.

**Objective:** To investigate into the growing use of ketamine for purposes other than anaesthesia, with an emphasis on its practical and clinical applications for PTSD, chronic pain, and depression that is resistant to treatment.

## MATERIALS AND METHODS

**Design:** The research design is cross-sectional and descriptive.

**Study Setting:** The study was carried out at Anesthesia Department, Lady Reading Hospital-MTI Peshawar, Pakistan.

**Duration**: The period from January, 2023 to June, 2023 was used for data collection and analysis.

**Inclusion Criteria:** The study included adult patients aged 18 to 65 who were treated with ketamine as part of their clinical management for treatment-resistant depression, chronic pain, or PTSD. Patients with follow-up data and at least two completed treatment sessions were chosen. Patients who voluntarily and knowingly consented to releasing their clinical data for research purposes were included in the study, regardless of their gender or socioeconomic background.

**Exclusion Criteria:** Any patient with a history of schizophrenia, bipolar mania, uncontrolled hypertension, an active substance use disorder, or a condition that precludes the administration of ketamine was excluded. Patients who were given ketamine only for procedural sedation or surgical anaesthesia without any intention of treating chronic pain or mental health issues were not included in the study. Patients with preliminary medical records or those who withdrew consent were excluded from the final analysis.

## METHODS

Data for this study were obtained through a retrospective chart review from the Anesthesia Department, Lady Reading Hospital-MTI Peshawar, Pakistan, Patient files from January, 2023 to June, 2023 were recurrently reviewed to identify patients who received ketamine therapy for PTSD, chronic pain, or treatment-resistant depression. Demographic data, diagnosis, indication for ketamine, dose, frequency, duration of ketamine therapy, and clinical outcomes were collected using a structured written data collection sheet to determine the effectiveness of ketamine therapy. Standardized clinical scales such as the Visual Analog Scale (VAS) for pain, the PTSD Checklist (PCL-5), and the Montgomery–Åsberg Depression Rating Scale (MADRS) were used to evaluate pre- and post-treatment status where available. Data were anonymized to maintain confidentiality. Descriptive statistics were applied to summarize patient characteristics and treatment outcomes. The primary outcome was improvement in clinical symptoms post-ketamine therapy, while secondary outcomes included patient tolerability and incidence of adverse effects during the study period.

## RESULTS

A total of 85 patient records were reviewed, out of which 70 met the inclusion criteria. Among the selected patients, 27 were treated for chronic pain, 23 for treatment-resistant depression (TRD), and 20 for post-traumatic stress disorder (PTSD). The cohort consisted of 41 females and 29 males, with a mean age of 39.2 years (range: 19–64). The average number of ketamine sessions per patient was 4.3, with most patients receiving low-dose intravenous infusions in a controlled outpatient or inpatient setting. Across all three conditions, clinical improvements were noted post-therapy.

Table 1: Demographic Characteristics of Participants

| Characteristic | Frequency (n = 70) | Percentage (%) |
|---|---|---|
| Gender | | |
| Male | 29 | 41.4% |
| Female | 41 | 58.6% |
| Age Group | | |
| 18–30 years | 19 | 27.1% |
| 31–45 years | 28 | 40.0% |
| 46–65 years | 23 | 32.9% |
| Diagnosis | | |
| Chronic Pain | 27 | 38.6% |
| Treatment-resistant Depression | 23 | 32.9% |
| PTSD | 20 | 28.5% |

Patients with chronic pain reported significant reductions in symptom severity, as measured by the Visual Analog Scale (VAS). The mean baseline VAS score was 8.1, which decreased to 3.4 after the final ketamine session. Among this group, 85% of patients experienced more than 50% reduction in pain scores, and 63% reported improved physical functioning.

Table 2: Pain Outcomes in Chronic Pain Patients (n = 27)

| Outcome Measure | Pre-Treatment Mean | Post-Treatment Mean | % Change |
|---|---|---|---|
| VAS Score | 8.1 | 3.4 | –58.0% |
| Functional Status Score | 4.3 | 6.9 | +60.5% |
| Responders (>50% relief) | 23 | — | 85.2% |

Among the patients with TRD, the Montgomery–Åsberg Depression Rating Scale (MADRS) showed a significant reduction in depression severity. The mean baseline MADRS score was 32.6, which dropped to 17.8 post-treatment. Approximately 74% of TRD patients were categorized as responders (≥50% symptom reduction), and 39% achieved remission (score <10). Side effects were generally mild and transient, including dissociation, nausea, and dizziness.

Table 3: Depression Outcomes in TRD Patients (n = 23)

| Outcome Measure | Pre-Treatment Mean | Post-Treatment Mean | Responders (%) | Remission (%) |
|---|---|---|---|---|
| MADRS Score | 32.6 | 17.8 | 74% | 39% |
| Dissociative Symptoms | Mild (78%) | — | — | — |
| Adverse Events | 9 patients | — | — | — |

In the PTSD group, 65% of patients showed a meaningful reduction in symptomatology, as measured by the PTSD Checklist (PCL-5). The mean score declined from 51.7 to 29.3. Patients

reported fewer nightmares, improved sleep, and better emotional regulation. Additionally, 60% of patients noted enhanced engagement during psychotherapy sessions when ketamine was used as an adjunct.

Table 4: PTSD Outcomes in Ketamine-Treated Patients (n = 20)

| Outcome Measure | Pre-Treatment Mean | Post-Treatment Mean | % Symptom Reduction |
|---|---|---|---|
| PCL-5 Score | 51.7 | 29.3 | –43.3% |
| Sleep Quality (self-rated) | 3.2 | 6.4 | +100% |
| Psychotherapy Engagement | Moderate (40%) | High (60%) | +50% |

Overall, 78.5% of all patients across diagnoses showed a clinically significant improvement after ketamine therapy. Side effects were present in 26% of patients, with the most common being transient dissociation (15%), nausea (6%), and dizziness (5%). There were no significant adverse consequences or dropouts due to intolerable symptoms. Those receiving additional therapies, such as psychotherapy or virtual reality, rated the experience more positively. This shows the potential for integrative care to improve ketamine's benefits. The results highlight the diverse treatment areas available, specifically for previously refractory patients. Pain, mood, and trauma all showed measurable improvements, which provides credibility to the use of ketamine in interdisciplinary treatment.

## DISCUSSION

The findings of this investigation align with a growing corpus of research that bolsters ketamine's potential as a therapeutic agent in addition to its conventional use as an anaesthetic. The drug's potential for multifaceted clinical use is demonstrated by the observed improvement in symptoms for patients with PTSD, treatment-refractory depression (TRD), and chronic pain. The results are consistent with earlier research showing that ketamine can reduce symptoms of difficult mental and pain conditions with a quick onset of action and long-lasting effects[1,2]. The analgesic and antidepressant effects of ketamine are thought to be mediated by N-methyl-D-aspartate (NMDA) receptor antagonism, a crucial step in glutamatergic signalling[3]. In many persistent pain syndromes, central sensitisation is a crucial process that can be broken by NMDA-receptor modulation[1].

According to the Visual Analogue Scale, 85% of participants in this study reported at least a 50% improvement in pain, demonstrating that patients with chronic pain continued to significantly reduce their pain levels. These findings align with those of Israel et al., who highlighted the critical function of ketamine in reducing allodynia and hyperalgesia in complex pain states[1]. Furthermore, ketamine's effects on synaptic plasticity and neurotrophic signalling pathways, which lead to the upregulation of brain-derived neurotrophic factor (BDNF), are probably the cause of the analgesic effects linked to TRD (4,5). The findings support these neurobiological insights, as 74% of TRD patients in the sample showed marked reductions in depressive symptoms following ketamine infusions. These results align with the growing consensus that ketamine provides a vital alternative for patients unresponsive to traditional monoaminergic antidepressants[5]. Furthermore, Muscat et al. advocate for integrative ketamine therapy that combines pharmacologic effects with psychological support, potentially enhancing outcomes in resistant cases[5].

Post-traumatic stress disorder has also emerged as a key area for ketamine's therapeutic application. By disrupting pathological fear memory consolidation and enhancing synaptic reorganization, ketamine facilitates trauma processing and emotional regulation[6,7]. In this study, patients with PTSD exhibited a 43% reduction in symptom severity as measured by the PCL-5. These results are consistent with Ragnhildstveit et al., who found that ketamine's capacity to weaken traumatic memory networks offers a novel approach for individuals not responding to standard therapies[4]. Notably, the addition of adjunctive psychotherapy and increased engagement during sessions, as seen in the sample, supports Halstead et al.'s findings on ketamine-assisted psychotherapy for race-related trauma[16]. One of the critical advantages of ketamine lies in its rapid onset, particularly in depressive and suicidal crises.

Traditional antidepressants often take weeks to achieve therapeutic effects, whereas ketamine has demonstrated symptom relief within hours[8]. This rapid response is particularly beneficial in acute settings or when immediate intervention is necessary. Kutz et al. even proposed ketamine's use in extreme environments, such as space missions, to manage acute suicidality, underscoring its versatility and adaptability[14]. This study also observed the incorporation of supportive tools such as virtual reality (VR) during ketamine administration, which was associated with improved patient satisfaction. Selinger et al also observed similar findings, highlighting that VR, together with ketamine, improved mood regulation and how patients perceived their experience during their treatment sessions[15]. These integrative approaches support the idea of personalized applications of ketamine therapy principles, such as in Gregoire's models of personalized interventions[6].

Nevertheless, ketamine also has limitations and challenges. Although the results were promising, there are potential adverse effects, including dissociation, nausea, and transient dizziness, which is why close monitoring is essential. In this study, side effects were seen in 26% of patients, but none were significant enough to discontinue treatment. Moreover, these figures appear consistent with previous literature, including Schwartz's military evaluation study, which also highlighted the importance of proper training and protocols for the field potential in administering subanesthetic ketamine[13]. Another challenge to consider is the sustainability of effects from ketamine. Although the safety and efficacy of acute response are well established, effects can last variable durations, and many patients require multiple sessions to obtain sustained symptom relief[12]. The addition of psychotherapy and follow-up care is critical to their continuation of benefits and reduction of relapse or symptom return. Walsh et al. pointed out its importance in their systematic review by advocating for treatment management through structured follow-up and combination therapy to reduce the probability of recurrence[10].

Ketamine therapy continues to encounter challenges relating to accessibility and stigma. Government-imposed barriers, insurance limitations, and its historic association with recreational drug use have prevented its widespread acceptance by traditional healthcare[12]. However, as research advances and perceptions change, ketamine is slowly beginning to be recognized as a legitimate treatment option. There is a great need for education and standardized clinical instructions to increase the broader application of psychiatry and pain management practices. The results align with previous preclinical and clinical trials, notably an overview of several studies by Boese et al., which concentrated on the pharmacological function of ketamine regarding the extinction of fear memory and modifications of emotional mental flexibility[11].

Moreover, the enantiomer (R)-ketamine has recently received much attention for its potential to offer the same clinical benefit with fewer side effects, as described by Shafique et al.[17]. These developments suggest another area to explore in the evolving landscape of refinement of ketamine-based treatment strategies. Despite the limitations of a retrospective study and a limited number of participants, the retrospective study adds important perspectives regarding ketamine's diverse clinical effects. Incorporating standardized outcome indicators, real-world data, and multiple diagnoses increases the amount of data to analyze. Future research could include longitudinal plans and randomized controlled trials to validate these findings and examine long-term safety and efficacy.

## CONCLUSION

This research illustrates the ever-growing therapeutic utility of ketamine, first as an anesthetic and now as a medicine showing positive clinical outcomes for chronic pain, TRD, and PTSD. The

data showed clinically important reductions in symptoms of all three conditions, with almost all patients reporting substantive improvements after several ketamine infusions. The rapid onset of ketamine-mediated symptom relief, its effects on neuroplasticity, and its unique pharmacological mechanism can provide immediate access to relief for individuals exhausted by unresponsive conventional treatments. Ketamine's side effects were generally mild and manageable, and the patients reported that they felt safe receiving infusions at a hospital-like clinical setting. Additionally, adjunct interventions like psychotherapy and virtual reality were associated with greater treatment satisfaction and outcomes. The use of adjunct interventions is an important factor to consider and plan for, as well as the ongoing consideration of the limitations of long-term efficacy, cost, and accessibility. Nonetheless, the data continues to support ketamine's role in contemporary psychiatry, as well as pain medicine. If professionals apply and proceed with caution, ketamine has the power to be a game-changing treatment option for multiple refractory, complex conditions in a multi-disciplinary healthcare approach.

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