Trials

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Adjunctive ketamine vs. buprenorphine in co-occurring major depressive disorder and opioid use disorder: a randomized, double-blind clinical trial assessing anxiety symptom severity and craving intensity

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Abstract

Background The concomitant presence of major depressive disorder (MDD) and opioid use disorder (OUD) poses a formidable clinical challenge, warranting effective interventions that address both psychiatric and addictive components.

Aims This study sought to compare the efficacy of adjunctive ketamine and buprenorphine in mitigating anxiety symptom severity and craving intensity in individuals with co-occurring MDD and OUD.

Methods A randomized, double-blind clinical trial was conducted, involving individuals meeting diagnostic criteria for both MDD and OUD. Participants were randomly assigned to receive adjunctive ketamine or buprenorphine, in conjunction with standard psychiatric and addiction treatments. Anxiety symptom severity and craving intensity were assessed using Hamilton Anxiety Rating Scale (HAM-A), and the Opioid Craving Scale after 2 h, 24 h, and 7 days.

Results The findings revealed distinct treatment trajectories, with ketamine demonstrating rapid and substantial reduction in anxiety symptom severity within hours of administration, accompanied by a pronounced decline in opioid craving intensity. In contrast, buprenorphine was associated with a more gradual but sustained improvement in anxiety symptoms over several days, paralleled by a modest initial reduction in opioid craving, followed by persistent attenuation.

Conclusions In conclusion, this randomized clinical trial provides evidence supporting the efficacy of adjunctive Ketamine and Buprenorphine in reducing anxiety symptoms and craving intensity in patients with co-occurring MDD and OUD.

Trial registration IRCT20211214053411N1.

Keywords Major depressive disorder, Opioid use disorder, Ketamine, Buprenorphine, Anxiety, Craving, Randomized clinical trial

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Introduction

Major depressive disorder (MDD) and opioid use disorder (OUD) represent significant public health challenges worldwide, each with profound individual and societal consequences [13, 56]. MDD, characterized by persistent feelings of sadness, hopelessness, and loss of interest or pleasure in activities, affects approximately 264 million people globally, making it a leading cause of disability [37, 49]. Similarly, OUD, characterized by compulsive opioid use despite harmful consequences, contributes to substantial morbidity and mortality, with an estimated 16 million individuals affected worldwide [35, 56]

One particularly challenging aspect of these disorders is their frequent co-occurrence. Studies indicate that individuals with MDD are at elevated risk for developing OUD, and vice versa [26, 47]. This comorbidity poses unique treatment challenges, as traditional interventions for MDD, such as selective serotonin reuptake inhibitors (SSRIs), may be less effective in individuals with OUD due to concerns about drug interactions and safety [19, 66]. Similarly, medications used to treat OUD, such as methadone or buprenorphine, may not adequately address the symptoms of depression [14, 52].

The co-occurrence of anxiety and MDD is a well-documented phenomenon, representing a significant challenge in clinical practice. Often, anxiety and MDD do not present in isolation; a substantial overlap exists in both their symptomatic presentations and underlying neurobiological mechanisms [69]. According to the National Institute of Mental Health (NIMH), this comorbidity is quite common, with an estimated 60% of individuals diagnosed with MDD also experiencing an anxiety disorder [29, 60]. Conversely, a significant portion of those with anxiety disorders, approximately 40%, are also diagnosed with MDD. This close relationship highlights the need for a nuanced understanding of both disorders and their interaction.

Research suggests that both anxiety and MDD are linked to abnormalities in brain regions critical for emotional regulation, notably the amygdala, responsible for processing emotions such as fear and threat, and the prefrontal cortex, which plays a role in executive function and mood regulation [18]. These neurobiological changes may contribute to the development and maintenance of anxiety symptoms in individuals with MDD, and vice versa.

The clinical implications of this comorbidity are also considerable, particularly concerning treatment outcomes. The presence of an anxiety disorder in an individual with MDD can negatively impact the effectiveness of treatments for MDD, and anxiety can complicate a patient's ability to fully engage with therapy, and even adhere to medication regimens. As a result, effective treatment often requires a multifaceted approach, sometimes incorporating both antidepressant and anxiolytic medications, as well as therapies tailored to address both the depressive and anxious symptoms [23, 30].

In recent years, there has been growing interest in the potential of adjunctive pharmacotherapies to improve outcomes in individuals with co-occurring MDD and OUD. Ketamine, a dissociative anesthetic with rapid-acting antidepressant properties, has shown promise in treating treatment-resistant depression (TRD) and acute suicidal ideation [15, 46]. Buprenorphine, a partial opioid agonist used in medication-assisted treatment (MAT) for OUD, has also demonstrated antidepressant effects in some studies [43, 44]. However, comparative data on the efficacy of ketamine versus buprenorphine in this population are limited.

Anxiety and craving are two interrelated phenomena that play significant roles in the maintenance of both MDD and OUD [45]. Anxiety symptoms, such as excessive worry, restlessness, and irritability, often co-occur with depression and can exacerbate opioid cravings and withdrawal symptoms in individuals with OUD [28, 54]. Craving, on the other hand, refers to an intense desire or urge to use opioids, which can be triggered by various internal and external cues, including negative affective states like anxiety [51, 55].

Ketamine and buprenorphine may exert differential effects on anxiety and craving due to their distinct pharmacological mechanisms of action [1]. Ketamine's rapid-acting antidepressant effects are thought to be mediated, at least in part, by its antagonism of the N-methyl-D-aspartate (NMDA) receptor and subsequent enhancement of synaptic plasticity and neurogenesis in key brain regions implicated in mood regulation, such as the prefrontal cortex and hippocampus [25, 48]. These neurobiological effects of ketamine may also mitigate anxiety symptoms by modulating glutamatergic neurotransmission and restoring dysfunctional synaptic connectivity in individuals with MDD and comorbid anxiety disorders [32].

In contrast, buprenorphine's effects on anxiety and craving may be mediated primarily through its actions at the mu-opioid receptor, where it acts as a partial agonist [5, 6]. By occupying mu-opioid receptors and attenuating the reinforcing effects of exogenous opioids, buprenorphine helps reduce opioid craving and withdrawal symptoms, thereby promoting abstinence and facilitating recovery in individuals with OUD [2, 7]. Additionally, buprenorphine's partial agonist activity may confer anxiolytic effects by stabilizing the dysregulated endogenous opioid system and restoring homeostasis in individuals with co-occurring anxiety and OUD [4, 6].

However, it is important to note that the effects of ketamine and buprenorphine on anxiety and craving are likely multifaceted and may involve interactions with other neurotransmitter systems implicated in mood and addiction, such as the serotonin, dopamine, and gamma-aminobutyric acid (GABA) systems [40, 65]. Moreover, individual differences in pharmacokinetics, genetic factors, and psychiatric comorbidities may influence treatment response and contribute to variability in outcomes across patients [42, 53].

Our hypothesis is that patients with MDD and OUD receiving adjunctive buprenorphine will experience a similar rapid reduction in their anxiety and craving score compared to those receiving adjunctive ketamine. The purpose of our study is to assess anxiety symptom severity and craving intensity in patients who received adjunctive therapy of ketamine or buprenorphine.

Methods

Trial design

The study employed a randomized, double-blind, double-arm, and active-controlled clinical trial design, adhering to the CONSORT guidelines for transparent reporting of trial methods.

Participants

Participants were recruited from Ebnesina Hospital in Shiraz, Iran. Inclusion criteria included patients aged 18–65 who admitted with a diagnosis of MDD according to DSM-5 criteria and concomitant OUD. Exclusion criteria comprised individuals using narcotic drugs for withdrawal control, those with a history of mania, depression with psychotic features, or critical internal diseases, and those with inadequate follow-up.

Intervention

Participants were randomly assigned to either Group A (ketamine) or Group B (buprenorphine). Group A received ketamine hydrochloride injection parenteral 50 mg/1 ml at a dosage of 0.5 mg/kg, diluted in normal saline 0.9 by intravenous pump for 40 min. Group B received 16 mg of sublingual buprenorphine in a single dose. Blinding was maintained through the administration of placebos, with participants in Group A receiving sublingual placebo tablets and Group B receiving normal saline 0.9% by intravenous pump for 40 min.

Outcomes

The primary outcomes were the change in symptom severity of anxiety, evaluated by the Hamilton Anxiety Rating Scale (HAM-A), and the severity of craving, assessed by the Opioid Craving Scale. Measurements were taken before the intervention, and then at 1 h, 24 h, and 1 week post-intervention. This specific timeframe was selected based on a combination of previous research, clinical expertise, and the expected pharmacokinetic behavior of the interventions being studied [38, 67].

Sample size

For this trial, the sample size for each intervention group and the placebo group has been recalculated to be 30 participants per group. This adjustment was made to maintain a power level of 80% and an error rate of 0.05, aligning with standard statistical practices in previous clinical research [3]. By increasing the sample size to 30 for each group, the study aims to enhance its ability to detect meaningful differences between the interventions and the placebo, ultimately strengthening the validity and reliability of the findings. We used a commonly cited threshold of 50% reduction in anxiety score as a guideline for determining clinically significant improvement [63]. Previous studies have shown that adjunctive ketamine can produce significant improvements in depression symptoms, with effect sizes ranging from medium to large [39, 57].We recalculated the sample size for this study to ensure that we have sufficient power to detect meaningful differences between the interventions and the placebo.

Randomization

Sixty-four eligible inpatients were randomly assigned to two groups using a computer-generated randomization sequence created by an independent statistician not involved in patient recruitment. This ensured the allocation sequence's transparency and integrity. A blocked randomization method, with blocks of 4 participants and no stratification, was employed. In this study, there were 16 blocks (total of 64 participants). All patients diagnosed with MDD and co-occurring OUD admitted to Ebnesina Hospital (Shiraz, Iran) were included in the study.

Blinding

In this study, the investigators are not able to know the treatment assignments. Also, the study participants are unaware of which treatment they are receiving. Blinding was maintained by using matched placebos and normal saline for the ketamine and buprenorphine groups, respectively.

Statistical methods

Data were analyzed using SPSS (version 20). The significance level for all tests was set at $p < 0.05$. Descriptive statistics, including means (M) and standard deviations (SD), were calculated for demographic and clinical characteristics. To compare final anxiety and craving scores

between groups while controlling for baseline scores and job status univariate ANCOVA was performed separately for HAM-A and Craving. Baseline scores (HAM-A, Craving) and job status were included as covariates. Effect sizes (partial η^2) were reported to determine the magnitude of group differences.

Ethical considerations

The study adhered to ethical standards outlined in the Declaration of Helsinki. Informed consent was obtained from all participants, and the study protocol was approved by the Shiraz University of Medical Sciences ethical review board.

Trial registration

This study was reviewed, approved, and monitored by the ethics committee of Shiraz University of Medical Sciences (License number: IR.SUMS.MED.REC.1400.333). This research has been registered in the Iranian Clinical Trials Registry (IRCT20211214053411N1) also. No changes occurred to methods after trial commencement.

Results

Participant flow

A CONSORT flow diagram (Fig. 1) details participant flow from screening to final analysis, showing the number of participants assessed for eligibility, randomized, and included in the analysis at each stage. Four patients were excluded after randomization but before treatment initiation due to unforeseen complications. Two developed induction mania, one was transferred to another hospital due to a COVID- 19 infection, and one experienced intolerable gastrointestinal symptoms and restlessness after receiving a high dose of buprenorphine and was subsequently withdrawn from the study.

Baseline characteristics

Baseline characteristics of participants in Group A (ketamine) and Group B (buprenorphine) are summarized in Table 1. While no significant differences were observed in age, sex, and education, there was a notable distinction in job status between the two groups ($p = 0.006$), indicating

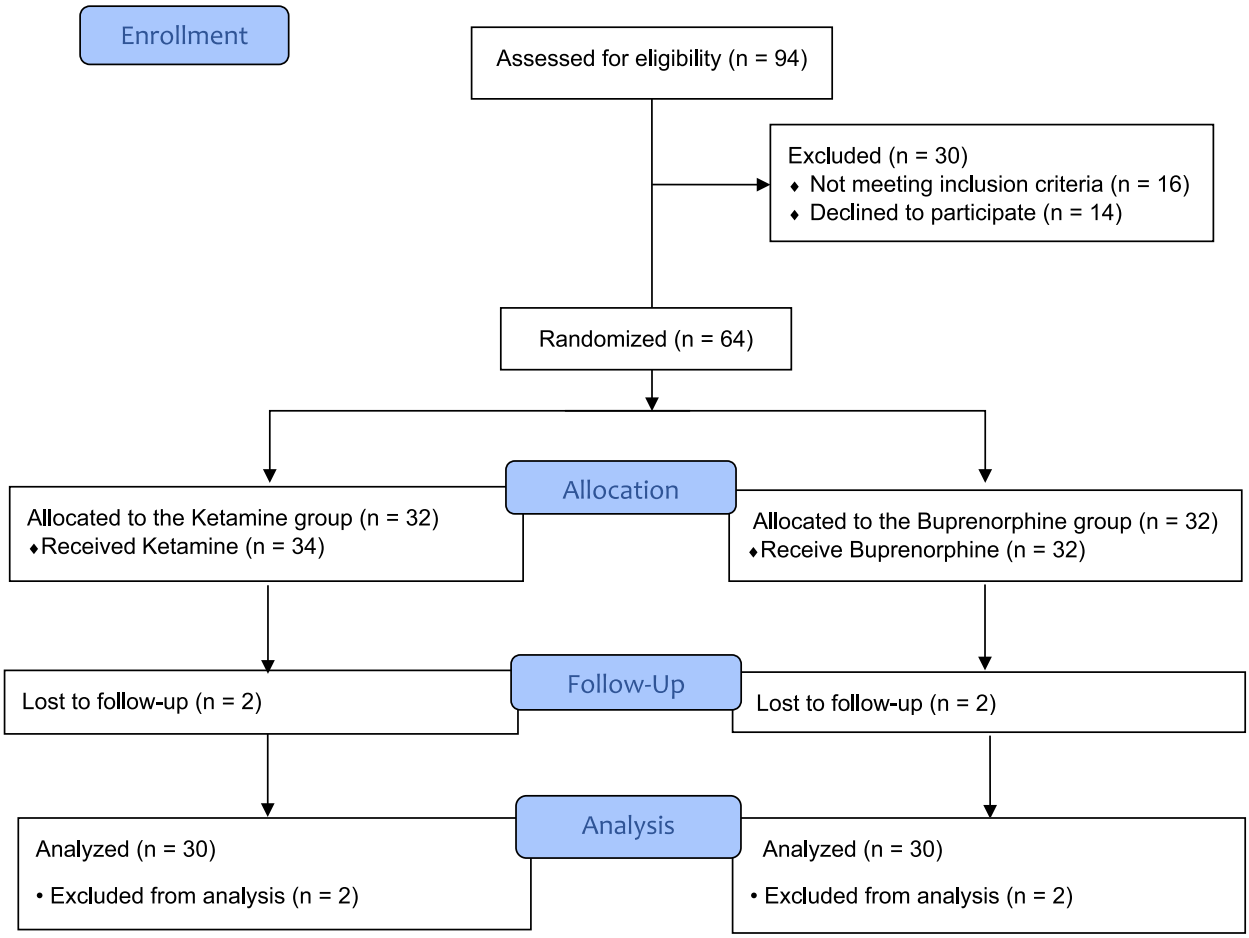

Fig. 1 CONSORT flow diagram

Table 1 Baseline characteristics

Baseline characteristics		Group		*p*-value
		Ketamine	Buprenorphine	
Age	Mean year	40.72 ± 11.19	40.79 ± 10.89	0.981
Sex	Male%	100.0%	96.7%	1.00
	Female%	0%	3.3%	
Education	Illiterate	3.3%	6.7%	0.575
	Under diploma	56.7%	56.7%	
	Diploma	26.7%	16.7%	
	B.A	6.7%	6.7%	
	M.S	3.3%	13.3%	
	M.A	3.3%	0.0%	
Job	No job	16.7%	60.0%	0.006
	Employed	13.3%	3.3%	
	Self employed	60.0%	30.0%	
	Retired	10.0%	6.7%	
Marriage	Single	26.7%	30.0%	0.320
	Married	73.3%	63.3%	
	Divorce	0.00%	6.7%	

Table 2 Changes in the Hamilton Anxiety Rating Scale (HAM-A) over time in both the ketamine and buprenorphine groups

HAM-A scores (mean ± SD)	Ketamine	Buprenorphine
Baseline	26.67 ± 8.711	24.77 ± 8.838
2 h later	11.97 ± 9.492	9.167 ± 8.762
24 h later	8.667 ± 8.180	6.467 ± 5.734
7 days later	6.533 ± 5.387	5.633 ± 6.419

a baseline imbalance. Subsequent analyses accounted for this discrepancy in job distribution to ensure robust and unbiased results.

Outcomes

Anxiety symptom severity

Table 2 presents the descriptive statistics for the Hamilton Anxiety Rating Scale (HAM-A) scores at different time points for both the Ketamine and Buprenorphine groups. A univariate analysis of covariance (ANCOVA) was conducted to assess the effects of treatment (ketamine vs. buprenorphine) on anxiety scores at 7 days, controlling for baseline anxiety and job status. The results, presented in Table 3, indicate that the effect of group on anxiety reduction was not statistically significant (F (1,54) = 0.316, p = 0.576, η^2 = 0.006). Neither baseline anxiety nor job status significantly influenced the final anxiety scores.

Craving intensity

Craving scores at different time points are presented in Table 4. The mean craving score at baseline was 7.04 ± 3.16 for the ketamine group and 6.41 ± 2.97 for the buprenorphine group. Craving scores decreased over time, with minimal differences between groups at 7 days.

ANCOVA results (Table 5) indicate that the effect of treatment on final craving scores was not statistically significant (F (1,50) = 0.010, p = 0.922, η^2 = 0.000). Neither job status nor baseline craving significantly influenced the outcome.

Adverse events

All participants were closely monitored for adverse events throughout the study period. Adverse events were assessed via regular clinical assessments and spontaneous reporting. Participants were asked to report any new or worsening symptoms.

Two patients developed induction mania after receiving ketamine and one experienced intolerable gastrointestinal symptoms and restlessness after receiving a high dose of buprenorphine and were subsequently withdrawn from the study.

Discussion

The study results revealed that both ketamine and buprenorphine demonstrated significant reductions in anxiety levels and opioid craving in patients with co-occurring MDD and OUD. The within-group analyses

Table 3 ANCOVA results for Hamilton Anxiety Rating Scale (HAM-A)

Source	SS	df	MS	*F*	*p*	Partial η^2
Corrected model	34.307	3	11.436	0.314	0.815	0.017
Intercept	126.327	1	126.327	3.469	0.068	0.060
Job	5.479	1	5.479	0.150	0.700	0.003
Baseline HAM-A (covariate)	21.133	1	21.133	0.580	0.449	0.011
Group (ketamine vs. buprenorphine)	11.510	1	11.510	0.316	0.576	0.006
Error	1966.314	54	36.413			
Total	4260.000	58				
Corrected total	2000.621	57				

Table 4 Changes in the Opioid Craving Scale over time in both the ketamine and buprenorphine groups

Opioid Craving Scale (mean ± SD)	Ketamine	Buprenorphine
Baseline	7.071 ± 3.102	6.533 ± 2.991
2 h later	0.6296 ± 1.668	1.000 ± 2.639
24 h later	0.3704 ± 0.6877	0.2333 ± 1.104
7 days later	0.6923 ± 0.9282	0.7333 ± 1.964

showed a substantial decrease in anxiety levels and opioid craving at 2 h, 24 h, and 1 week post-intervention compared to baseline for both treatment groups. These results suggest that both ketamine and buprenorphine were effective in addressing anxiety symptoms and diminishing opioid craving among the study participants.

The lack of statistically significant differences between the two treatment groups in terms of their effects on anxiety symptom severity and craving intensity implies that both adjunctive therapies—ketamine and buprenorphine—hold promise for mitigating these symptoms in individuals with co-occurring MDD and OUD. These findings have important implications for the management of this vulnerable population and point to the potential effectiveness of both treatments in addressing these interconnected aspects of co-occurring disorders.

The positive impact of buprenorphine observed in our study aligns with existing literature [5, 8]. Previous investigations, have highlighted buprenorphine's potential in reducing suicidal ideation and craving symptoms in individuals with MDD and OUD [2, 8]. Preclinical trials and systematic review further support its anxiolytic and antidepressant effects, emphasizing its potential as a valuable treatment option for this unique patient population [11, 31, 34, 36].

The anti-anxiety effects of buprenorphine, a partial opioid agonist, are thought to be mediated through its interactions with the brain's opioid receptors, particularly the mu-opioid receptors [10, 58]. Buprenorphine's unique pharmacological profile as a partial agonist at these receptors contributes to its anti-anxiety properties through several underlying mechanisms. Firstly, buprenorphine's partial agonist activity at the mu-opioid receptors results in a ceiling effect on respiratory depression and sedation, distinguishing it from full opioid agonists. This distinct pharmacological feature allows buprenorphine to provide anxiolytic benefits without the pronounced sedative and respiratory depressive effects associated with traditional opioids, making it a safer alternative for individuals with co-occurring anxiety and opioid use disorder. Furthermore, buprenorphine's partial agonism at the mu-opioid receptors also leads to its unique pharmacodynamics profile, characterized by a prolonged duration of action and a slower dissociation from the receptor compared to full agonists [62]. This sustained and stable binding to the mu-opioid receptors may contribute to the gradual but sustained reduction in anxiety observed with buprenorphine, reflecting its ability to modulate the brain's stress and anxiety pathways over an extended period.

Moreover, buprenorphine's interactions with the kappa-opioid receptors (KORs) and its modulation of the dynorphin system are implicated in its anti-anxiety effects [41]. KORs are involved in the regulation of stress responses and aversive behaviors, and buprenorphine's activity at these receptors may contribute to its anxiolytic properties. Specifically, as a partial agonist at KORs, buprenorphine may modulate the release of the endogenous opioid peptide dynorphin, which plays a role in stress regulation and emotional processing. By influencing the activity of the dynorphin-KOR system, buprenorphine may exert anxiolytic effects through its impact on stress-related neurocircuitry and the modulation of fear and anxiety responses. These multifaceted interactions with the mu-opioid receptors, as well as the kappa-opioid receptors and the dynorphin system, underscore the complex pharmacological basis of buprenorphine's anti-anxiety effects and provide a comprehensive framework

Table 5 ANCOVA results for craving scores

Source	SS	df	MS	*F*	*p*	Partial η^2
Corrected model	0.728	3	0.243	0.092	0.964	0.005
Intercept	7.302	1	7.302	2.764	0.103	0.052
Job	0.034	1	0.034	0.013	0.910	0.000
Baseline craving (covariate)	0.662	1	0.662	0.250	0.619	0.005
Group (ketamine vs. buprenorphine)	0.026	1	0.026	0.010	0.922	0.000
Error	132.106	50	2.642			
Total	161.000	54				
Corrected total	132.833	53				

for understanding its mechanisms of action in addressing anxiety within the context of co-occurring MDD and OUD [33]. The anti-craving effects of buprenorphine in the context of opioid use disorder (OUD) stem from its complex pharmacological actions on the brain's opioid receptors and related neurobiological pathways. Buprenorphine's efficacy in reducing opioid cravings is primarily attributed to its high-affinity partial agonism at the mu-opioid receptors, which allows it to competitively occupy these receptors and exert a modulatory influence over the neurocircuitry involved in reward processing and addiction [12]. By binding to and activating mu-opioid receptors, buprenorphine mitigates the intensity of opioid cravings by attenuating the signaling cascades associated with opioid reinforcement and the subjective experience of craving [27]. This partial agonist activity, coupled with its ceiling effect on respiratory depression and euphoria, renders buprenorphine an effective pharmaceutical intervention for managing opioid cravings without inducing the same degree of euphoria and reinforcing effects as full opioid agonists, thus supporting sustained recovery from OUD [22].

Furthermore, buprenorphine's pharmacodynamic profile as a partial agonist at the mu-opioid receptors contributes to its anti-craving effects through its intrinsic opioid receptor regulation. By acting as a partial agonist, buprenorphine can effectively normalize dysregulated opioid receptor activity, providing a level of opioid receptor stimulation that is sufficient to alleviate withdrawal symptoms and reduce cravings, while simultaneously blunting the reinforcing effects of exogenous opioids [70]. This nuanced modulation of the opioid system underlies buprenorphine's capacity to address the complex interplay of opioid withdrawal, cravings, and reinforcement, offering a pharmacological foundation for its anti-craving effects and reinforcing its utility as an integral component of medication-assisted treatment for individuals with OUD.

Similarly, ketamine, an approved emergency treatment for depression in suicidal patients, exhibited notable effects in our study. Consistent with prior research, ketamine demonstrated a substantial reduction in cravings, supporting its potential in the management of substance use disorders (SUD) [31]. The anti-anxiety effects of ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, are thought to be primarily mediated by its modulation of glutamatergic signaling and the downstream effects on synaptic plasticity and neuroplasticity within the brain [64]. Ketamine exerts its rapid and robust anti-anxiety effects by antagonizing NMDA receptors, leading to a cascade of neurobiological events that result in enhanced synaptic connectivity and the restoration of neural circuitry associated with emotional regulation and stress response [21]. Specifically, ketamine's blockade of NMDA receptors is believed to disinhibit and activate α-amino- 3-hydroxy-5-methyl- 4-isoxazolepropionic acid (AMPA) receptors, initiating a series of molecular and cellular mechanisms that promote the release of brain-derived neurotrophic factor (BDNF) and the activation of mammalian target of rapamycin (mTOR) signaling, ultimately fostering synaptic growth and connectivity in key brain regions implicated in anxiety, such as the prefrontal cortex and the hippocampus [9]. This rapid and profound modulation of glutamatergic neurotransmission and neuroplasticity underpins ketamine's unique mechanism of action in swiftly alleviating anxiety symptoms, offering a novel therapeutic approach for individuals with co-occurring major depressive disorder and opioid use disorder [61].

Moreover, ketamine's blockade of NMDA receptors prompts the disinhibition of α-amino- 3-hydroxy-5-methyl- 4-isoxazolepropionic acid (AMPA) receptors, triggering a cascade of intracellular signaling pathways involving brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR), which promote synaptic plasticity and connectivity in regions such as the prefrontal cortex and the nucleus accumbens. This rapid and enduring modulation of glutamatergic transmission and synaptic architecture underlies ketamine's unique mechanism of action in swiftly ameliorating opioid cravings, offering a promising avenue for addressing the complex interplay of opioid use disorder and co-occurring psychiatric conditions [17, 68].

Ketamine has also proved to provide rapid relief from depressive symptoms, often seen even after only a few hours after its administration [59]. However, relief from depressive symptoms is generally short-lived, lasting for about one week unless repeated infusions are given. Unlike the rapid loss of effectiveness after one treatment, repeated administrations of ketamine can sustain the relief from the symptoms for some length of time. Various reports suggest repeated infusion regimens can provide lasting benefits; however, the length of the after-treatment effects is not known [24]. Empirical studies indicate that the ability of ketamine is the potential for its facilitation of synaptic formation and increased glutamate receptor availability in the central nervous system, elements possibly contributing towards its antidepressive qualities [20]. These changes could help sustain mood improvement over the long-term; however, the long-term consequences remain under study. Nonetheless, long-term use could cause physical and psychological dependence, compromising its therapeutic benefits [50]. Chronic use by individuals can involve shifts in mood,

cognitive impairments, and several other negative consequences potentially interfering with the effectiveness of treatment.

Buprenorphine is combined with other treatment for individuals dependent on opioids or those not helped by normal antidepressants. Depressive symptoms supposedly improve when treated with buprenorphine, but its effectiveness relative to ketamine is unknown [16]. We know very little about the effectiveness of buprenorphine for the treatment of depression over the long term. It may benefit some populations, but its effectiveness for the treatment of depression over the long term is unknown.

Despite the concordance of our results with existing literature, the need for further investigation is evident. This study, while providing valuable insights, has limitations that warrant consideration. Future research should extend study periods, include more diverse samples (particularly women), and incorporate placebo-controlled groups to enhance the robustness and generalizability of the findings. While the study provides valuable insights, caution is necessary when generalizing the findings. The relatively small sample size and the single-center design limit the external validity of the results. The study focused on a specific demographic in a particular setting, potentially restricting the applicability of the findings to broader populations. Future research should aim for larger, more diverse samples across multiple centers to enhance the generalizability of the results.

Several limitations merit consideration. The study's short-term follow-up may not capture the long-term effects and sustainability of the observed improvements. Additionally, the potential for selection bias and unmeasured confounders could influence the results. One important consideration is the fact that this study did not incorporate a control group treated regularly. Since we do not have the group for the purpose of comparing, we cannot say for sure whether the changes over the study period were due only to the intervention. In the future, the impact of the intervention can be seen by including a control group.

Conclusion

In conclusion, this randomized clinical trial provides evidence supporting the efficacy of adjunctive Ketamine and Buprenorphine in reducing anxiety symptoms and craving intensity in patients with co-occurring MDD and OUD. The findings suggest that both interventions hold promise as valuable additions to the treatment plan for this challenging patient population. However, further research with larger sample sizes and longer follow-up periods is warranted to confirm these findings and elucidate the mechanisms underlying the observed effects.

Competing interests

All authors have no conflicts of interest with the research or writing of this paper.

Supplementary Information

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Supplementary Material 1.

Authors' contributions

All authors contributed to the conception or design of the study or to the acquisition, analysis, or interpretation of the data. All authors drafted the manuscript, or critically revised the manuscript, and gave final approval of the version that was submitted for publication. All authors agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Declarations

Competing interests

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