Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

REVIEW ARTICLE

Efficacy and safety of ketamine for the treatment of depressive symptoms in palliative care: a systematic review

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Objectives: Ketamine has a fast onset of action that may offer a paradigm change for depression management at the end of life. We aimed to synthesize evidence regarding the safety and efficacy of ketamine in depression treatment within a broad palliative care concept.
Methods: We searched seven databases and included studies on the safety and efficacy of ketamine for depression treatment in patients diagnosed with any life-threatening disease. We also conducted a narrative review of the evidence.
Results: Among 2,252 screened titles and abstracts, we included 32 studies in our final synthesis: 14 case reports, two case series, two quasi-experimental studies, and seven randomized clinical trials (RCTs), as well as data from three unpublished clinical trials and seven cases from four larger case series. Most case reports reported a robust effect; however, the larger studies reported conflicting findings. Five RCTs reported positive outcomes; however, four of them were focused on a perioperative setting. Two negative studies did not primarily focus on depression and did not apply severity cutoffs.
Conclusion: Although ketamine is generally safe and potentially useful, its efficacy in palliative care settings remains unclear. It may be a reasonable alternative for perioperative depression in oncological patients.

Keywords: Ketamine; antidepressive agents; palliative care; depression; mood disorders

Introduction

Depressive disorders are highly prevalent in the adult population, with major depressive disorder (MDD) having an estimated worldwide annual prevalence of 4.7%.[1] Moreover, they exert a significant burden, with MDD contributing to 2.5% of global disability-adjusted life years (DALYs).[2] Chronic medical conditions and pain increase susceptibility to depression; accordingly, the estimated prevalence of MDD among patients with cancer undergoing palliative care is 7-49%.[3]

Monoaminergic antidepressants have been the primary pharmacological treatment for MDD for > 80 years. Their efficacy over placebo has been described in meta-analyses of adult patients with depression in the general population[4] and in palliative care settings.[5] However, their unfavorable remission rates and extended time-to-remission windows ($\geq$ 4-8 weeks)[6] limit their utility at the end of life, which strongly features depression and requires prompt symptom reduction given patients' short life expectancy.

Accordingly, there have been extensive efforts to shorten the response time of depression treatment in this setting. Methylphenidate, which is routinely used to treat mood disorders in the general population, is frequently prescribed as an off-label intervention for rapid relief of depressive symptoms. Some studies on patients receiving palliative care have reported an early response, starting at 3 days.[7] However, there have only been a few randomized clinical trials (RCTs), with inconsistent results.[7-9]

Glutamatergic drugs are a potential new standard treatment for depression. Ketamine, an N-methyl-D-aspartate (NMDA)-receptor noncompetitive antagonist, was developed as an anesthetic[10] and has been increasingly used as an antidepressant in recent practice, even though this indication was first reported > 20 years ago.[11,12] Intranasal esketamine has been approved for depression treatment by the United States Food and Drug Administration (FDA), as well as other regulatory agencies.

Ketamine has a higher response rate (65-70%)[13] and a faster onset of action than monoaminergic antidepressants. Although the antidepressant effects of ketamine can appear as early as < 1 h after administration,[14] they peak at approximately 24 h and last for 7 days.[15] Additionally, these profiles vary according to the administration route, with oral ketamine having a more delayed onset.[16]

Ketamine has been extensively studied in palliative care settings, mainly as a continuous subcutaneous (SC) infusion for adjunctive treatment of opioid-unresponsive oncologic pain.[17] Moreover, two reviews examined different aspects of administering ketamine and other psychedelic drugs in end-of-life care, including studies on pain and mental disorders.[18,19] Although these studies focused on the potential of ketamine, its utility in depression remains unclear, since it has been underused and reserved for treatment-resistant scenarios, probably due to a lack of robust safety data.

Given the growing body of evidence regarding the use of ketamine in psychiatry, we aimed to describe the use of this agent as an antidepressant in palliative care settings, since a fast-acting drug may provide a paradigm change in such a time-sensitive scenario. Specifically, we aimed to review studies on the safety and/or efficacy of ketamine (or any of its enantiomers) for depression treatment within a broad concept of palliative care according to the World Health Organization (WHO) definition, i.e., interventions promoting the quality of life of people suffering from life-threatening illnesses.[20]

Methods

Search strategy

We searched seven databases (PubMed/MEDLINE, Cochrane, Web of Science, EMBASE, Scopus, PsycINFO, and ClinicalTrials.gov) using strategies developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] Moreover, we screened the references of the selected articles, contacted several authors, and investigated the gray literature. Appendix 1 shows the search strategies.

Inclusion criteria

Study type

Clinical trials, cohort studies, case-control studies, case series, and case reports were included.

Mental health diagnosis

Participants must present depressive symptoms or be at risk of depression. Symptoms must be measured using validated symptom scales and/or qualitatively described (in case reports).

Condition subject to palliative care

To capture the broad spectrum of palliative care, we searched terms regarding the most common chronic, progressive, life-threatening illnesses, rather than only specific terms such as "palliative care" and "end-of-life." Accordingly, we selected 10 conditions that may render the patient a candidate for palliative care, based on the minimal estimate proposed by Rosenwax et al.[22] This list was used to broaden our search. Nonetheless, we included studies involving any life-threatening illness at any stage.

Intervention

Pharmacological treatment with ketamine or its enantiomers (S-ketamine, also known as esketamine, or R-ketamine, also known as arketamine) via any route of administration and with any treatment/follow-up duration, as monotherapy or adjunctive medication. We included studies with placebo controls, drug comparisons, or no controls.

Outcomes

We included studies that reported depressive symptom outcomes, including changes in severity scale scores, response or remission rates, or subjective improvements in mood and behavior.

Language

We included studies published in English, Portuguese, or Spanish.

Exclusion criteria

We excluded studies only published as conference posters or oral sessions, letters to the editor without complete descriptions of the original data, review articles, clinical trial protocols, studies involving patients not clearly subject to palliative care (including patients undergoing elective non-cancer surgery), and studies not available in the selected languages.

Procedures

This review was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021240763). The initial and subsequent literature searches were performed in May 2021 and February 2022, respectively. Abstract screening, full-text screening, and quality assessment were performed independently by two authors (MGB and GTG), with conflicts being resolved by a third author (APJ). The authors performed data extraction and synthesis. All review stages were performed using the Covidence[23] application. For quality assessment, we used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports, Case Series, and Quasi-Experimental Studies,[24] as well as version 2 of the Cochrane Risk-of-Bias (RoB 2) tool for randomized trials.[25]

Results

We initially imported 3,933 entries into Covidence. After removing duplicates, 2,246 titles and abstracts were

screened. We also added three new records via manual searches, and retrieved unpublished data from three trials at ClinicalTrials.gov and by contacting the authors. Subsequently, 73 entries were included in the full-text review, with 32 studies being ultimately included in the analysis. Figure 1 shows the PRISMA flowchart.

Risk-of-bias (RoB) assessment

The included studies showed a generally low RoB considering the specific limitations of some study designs, including case reports and series. Table 1 summarizes the RoB assessment of the RCTs.

Case reports

We included 14 case reports on 16 patients (one study reported two patients, one study reported three patients, and two reports described the same patient at different time points).[33-45] These are summarized in Table 2.

We also included seven relevant patients from other case series. A series of five cases on the effect of ketamine in reducing L-DOPA-induced dyskinesia included one patient with depression.[46] This 84-year-old man with Parkinson's disease received a 65-h intravenous (IV) infusion of ketamine, which was titrated from 0.05 mg/kg/h to 0.15 mg/kg/h. The patient showed subjective "dramatic improvement" (the patient was suicidal before infusion and only mildly depressed on subsequent follow-up visits). No adverse effects were observed.

Another series of five cases reported the effectiveness of ketamine in patients resistant to electroconvulsive therapy or transcranial magnetic stimulation. Among them, one was diagnosed with breast cancer.[47] This 51-year-old woman received a single 0.5 mg/kg IV ketamine infusion. Her Montgomery-Asberg Depression Rating Scale (MADRS)[48] score was 38 at 2 h before infusion, which dropped to 27 at 120 min after infusion but returned to 39 after 24 h upon treatment discontinuation. She showed mild dissociative effects during infusion, with no other side effects.

A series of four cases reported the effect of low-dose ketamine on critical illness, with one patient having depression.[49] This 55-year-old man with acute respiratory distress syndrome received a 70-h infusion of 3 μg/kg/min IV ketamine. His depression subscale of the Hospital Anxiety and Depression Scale (HADS-D)[50] score was 12 at baseline, 9 after 24 h of treatment, and 8 after 24 h of treatment. There were no psychotomimetic effects during infusion.
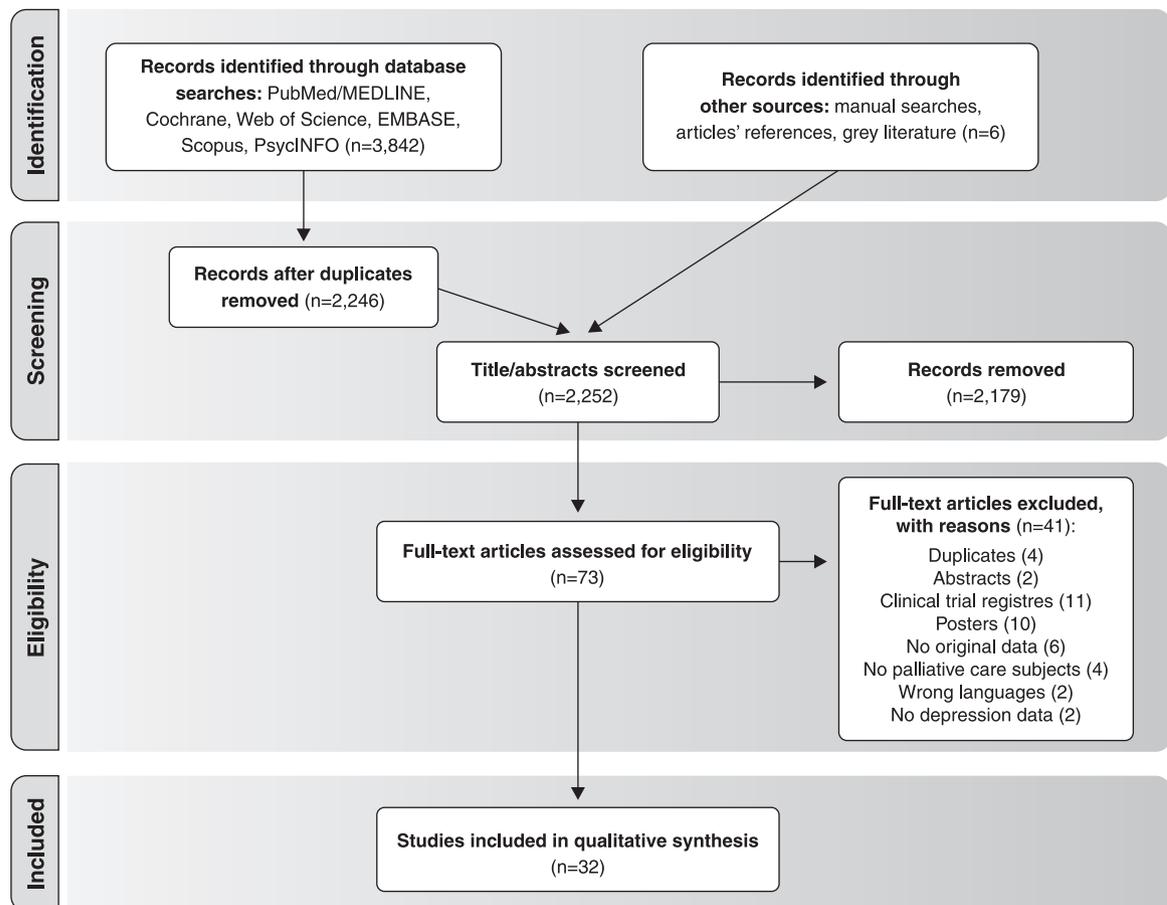

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1 Risk-of-bias (RoB) assessment for the included randomized clinical trials (RCTs)

Author	Randomization processes	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of result	Overall RoB
Salas[26]	Low	Low	Low	Low	Low	Low
Wang[27]	Low	Low	Low	Low	Low	Low
Fan[28]	Low	Low	Low	Low	Low	Low
Xu[29]	Low	Low	Low	Low	Low	Low
Fallon[30]	Low	Low	Low	Low	Low	Low
Liu[31]	Low	Low	Low	Low	Low	Low
Zhou[32]	Low	Low	Low	Low	Low	Low

Bryant et al.[51] reported six patients treated with 0.5 kg/kg IV ketamine for geriatric depression. Among them, four patients had diseases eligible for palliative care. Infusions were administered twice weekly for two to four infusions and then every 2-6 weeks.

One patient responded to ketamine but relapsed with alcohol dependence. Two patients responded initially, but this effect was not sustained. The fourth patient received five infusions and did not show any improvement. Treatment was discontinued in all patients.[51]

Case series

We included three case series that reported quantitative and qualitative depressive symptom assessments, which are summarized in Table 3.

Iglewicz et al.[52] reported on 31 hospice inpatients aged 44-89 years (mean = 68 years) who received ketamine for depression. Among them, 77% had a cancer diagnosis, while the remaining patients had coronary disease, liver failure, and other conditions. Positive therapeutic outcomes on the Clinical Global Impression (CGI)[55] scale were more common than negative ones at days 0-1, 2-3, and 4-7 after dosing. Regarding side effects, more patients had positive outcomes than negative outcomes at all time points, and all side effects were psychiatric (disorientation, sedation, and hallucinations).

Latuga et al.[53] reviewed the charts of three hospice patients aged 49-83 years. Two patients had a cancer diagnosis while one had a cirrhosis diagnosis. Patients received a single dose of 0.5 mg/kg SC ketamine injection followed by daily 0.5 mg/kg oral doses of ketamine. One patient had a PHQ-4[56] of 12 at baseline; after 2 days, he reported a notable increase in energy and sense of well-being. On day 7, his PHQ-4 score was 0 and remained 0 despite his worsening physical disability.

Another patient had a PHQ-4 score of 6 at baseline. On day 4, the oral ketamine dose was decreased from 30 mg to 5 mg due to somnolence. His PHQ-4 score was 1 on day 7 and remained between 1 and 3 until day 50, when he began experiencing mood fluctuations until he died. At baseline, the last patient had a depression score of 10/10, with no PHQ-4 scores being recorded. On day 3, her depression rating and PHQ-4 scores were 6/10 and 12, respectively. On day 12, her depression rating and PHQ-4 scores were 6/10 and 7, respectively. On day 19, her PHQ-4 score was 1. She developed delirium and lethargy on day 37 and died. These patients reported nausea,

drowsiness, fatigue, sleepiness, and feeling "strange" and "floating." One patient showed increased blood pressure at 20 minutes post-injection. Overall, ketamine was well tolerated, and the side effects were self-limited.

Rosenblat & Li[54] reported on three hospice patients aged 60-80 years who requested medical assistance in dying (MAiD) and received intranasal ketamine doses (50-150 mg) at 3-day intervals. One patient with cancer, who had a poor prognosis, responded to ketamine and had improved motivation, drive, and energy. She went to a movie and restaurant as well as enjoyed playing games on a smartphone. She improved her guilt and indecisiveness; furthermore, she had a strengthened desire for MAiD. The patient reported transient drowsiness and vivid dreams. Another patient with ovarian cancer, who had a poor prognosis, reported, "Wow, I feel a lot better. I am so glad I finally decided to do the study," after the first ketamine dose, which was confirmed by her daughter. She withdrew her request for MAiD after realizing that it was largely driven by guilt and low self-worth. The patient reported transient drowsiness and dizziness. A third patient reported significantly reduced depressive symptoms after ketamine administration. He entertained friends in his hospital room and agreed to engage in a psychotherapeutic life review. He remained firm in his decision to receive MAiD.[54] The patient reported transient drowsiness and confusion.

Overall, all case series reported positive therapeutic effects. Iglewicz et al.[52] reported an early response (1-3 days), which was sustained for 7 days; Latuga et al.[53] reported a robust and sustained improvement that lasted 1-7 weeks; Rosenblat & Li[54] reported subjective mood improvement for all patients within the treatment timeframe (9 days).

Quasi-experimental studies

We included two quasi-experimental studies, which are summarized in Table 4. A non-randomized study by Falk et al.[51] included 16 patients in a specialized palliative care unit. Among them, eight patients received the intervention (a single IV infusion of 0.25 mg/kg esketamine), and eight patients were used as controls (those not requiring ketamine for pain control, who received standard care). The mean age was 52 and 55 years in the intervention and control groups, respectively. The main diagnoses were multiple cancer types and HIV infection. There was no significant effect on State Trait Anxiety Depression

Table 2 Summary of findings from case reports

Author	n	Age (years)	Sex	Palliative care diagnosis	Intervention (dose, route, duration)	Results (depression)	Side effects	Comments and follow-up
Zanicotti[33,42]	1	36	Female	Metastatic ovarian cancer	Repeated IM ketamine (weekly for 10 months, 1 mg/kg)	MADRS reduction from 24 at baseline to 7 at 1 h after the first injection (71% improvement)	Moderate but tolerable dissociative effects Improved tolerability over time and stable vital signs	Sustained remission (MADRS <10) for 10 months on ketamine and 8 more months after discontinuation
Rocha[40]	1	76	Female	Alzheimer's disease	Repeated SC ketamine (eight doses, 0.5-0.75 mg/kg)	CGI-S reduction from 7 at baseline to 1 after two doses (3 days)	Light somnolence during ketamine sessions, no other side effects	Sustained remission for six more doses and 1 month after discontinuation
Stefanczyk-Sapieha[45]	1	50	Male	Hormone-refractory prostate cancer	Repeated IV ketamine (two doses, 10 days interval, 0.5 mg/kg)	BDI and HAMD-17 reduction from 25 and 30 at baseline to 11 and 15 at 6 h after the second dose (56% and 50% improvement)	A brief episode of visual hallucinations during the second dose	Effects wore off quickly
Rodríguez-Mayoral & Domínguez-Ocadio[35]	1	39	Female	Cervical epidermoid carcinoma	Single dose of IV ketamine (0.5 mg/kg)	BEDS reduction from 18 at baseline to 5 on day 17 (72%)	No side effects	
Swiatek[36]	1	62	Male	Liver failure	Repeated oral ketamine (nine daily doses, 0.25-0.5 mg/kg)	HADS-D reduction from 16 at baseline to 10 after 48 h (38% improvement)	No safety measures reported	Mood worsened due to aggravated clinical condition Treatment was discontinued to focus on comfort
Barbosa[37]	1	65	Male	Undifferentiated metastatic abdominal tumor	Repeated SC ketamine (four doses, twice a week, 0.5-0.75 mg/kg)	MADRS reduction from 30 at baseline to 9 on day 7 (70% improvement)	Stable vital signs, intense dissociative symptoms without discomfort	Patient died on day 11
Cortiñas-Saenz[43]	1	42	Female	Breast cancer with bone metastasis	Repeated IV ketamine (a single dose followed by five daily doses, 0.3-0.5 mg/kg)	HAMD-17 reduction from 22 at baseline to 13 (41% improvement) 4 days after discontinuation	Mild nausea and confusion	Sustained improvement for 2 weeks until his death
Sexton[38]	1	64	Male	Metastatic anaplastic thyroid cancer	A single continuous IV ketamine infusion (2 weeks, 0.2 mg/kg/h)	PHQ-9 24 at baseline, not reported at follow-up Remission of suicidal ideation and significant qualitative improvement on day 5	Two episodes of worsening pain during the infusion	Sustained improvement for 2 weeks until his death
Rajagukguk & Lee[39]	1	Late 40s	Male	Jejunal adenocarcinoma	A single infusion of IV ketamine (0.5 mg/kg)	Self-assessment of depression decreased from 8/10 to 0/10 in 24 h Significant qualitative improvement	Drowsiness	Worsened after 5 days, refused treatment
Litvan[41]	1	74	Female	Mixed dementia (Alzheimer's + vascular)	12 sessions of ECT with esketamine anesthesia	Remission of catatonic symptoms	No safety measures reported	
Irwin[34]	2	64	Female	COPD, respiratory failure	Repeated oral ketamine (two doses, 30 days interval, 0.5 mg/kg)	HAM-D-17 and HADS-D reduction of 66 and 50% at day 15	No side effects reported	No response to the second dose
		70	Male	Metastatic prostate cancer	A single dose of oral ketamine (0.5 mg/kg)	HAMD-17 and HADS-D reduction of 57 and 45% on day 8	No changes in scores for adverse effects and cognitive status	Physical deterioration on day 13, could not participate in the assessments
McNulty & Hahn[44]	1	44	Male	Heart failure and COPD	A single SC ketamine injection (0.5 kg/kg) followed by daily oral ketamine (0.5 mg/kg)	Improvement in self-assessed depression from 8/10 to 0/10 in 60 min	No side effects	Sustained remission under oral ketamine for 2 months

BDI = Beck Depression Inventory; BEDS = Brief Edinburgh Depression Scale; CGI = Clinical Global Impression; COPD = chronic obstructive pulmonary disease; ECT = electroconvulsive therapy; HADS = Hospital Anxiety and Depression Rating Scale; HAMD-17 = Hamilton Depression Rating Scale; IM = intramuscular; IV = intravenous; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; SC = subcutaneous.

Table 3 Summary of findings from case series

Author(s)	n	Age (years)	Sex	Palliative care diagnosis	Intervention (dose, route, duration)	Depression measures	Results (depression)	Side effects	Comments and follow-up
Iglewicz[52]	31	44-89	Both	Multiple (cancer and non-cancer)	Single (n=22) or multiple (n=9) doses of 0.5 mg/kg oral (n=29), SC (n=1) or oral + SC (n=1) ketamine	CGI score at baseline and days 0-1, 2-3, 4-7, and 8-21	Positive therapeutic outcomes for depression were more common (93%) than negative therapeutic outcomes at days 0-1 ($p < 0.001$), 2-3 ($p < 0.001$), and 4-7 ($p < 0.05$)	No serious side effects More patients had positive therapeutic outcomes than negative therapeutic outcomes ($p < 0.001$ at days 0-1 and 8-21, and $p < 0.05$ at days 2-3 and 4-7)	
Latuga[53]	3	76	Male	Metastatic pancreatic adenocarcinoma	A single dose of SC ketamine (0.5 mg/kg) followed by repeated oral ketamine doses (daily, 0.5 mg/kg)	PHQ-4	Reduction from PHQ-4 12 at baseline to PHQ-4 0 on day 7	Somnolence, nausea, drowsiness, fatigue, sleepiness, feeling "strange" and "floating" Increased blood pressure at 20 min post-injection in one patient	Sustained remission with 0 on PHQ-4, died on day 50
		83	Male	End-stage alcoholic cirrhosis			Reduction on PHQ-4 from 6 at baseline to 1 on day 7		PHQ-4 remained between 1 and 3, died on day 139
		49	Female	Metastatic ovarian cancer			Reduction of PHQ-4 from 12 on day 3 to 1 on day 19		Sustained until she died on day 37
Rosenblat & Li[54]	3	67	Female	Cancer	Repeated IM ketamine (three doses, 3 days interval, 50-150 mg)		Improved guilt, indecisiveness and strengthened desire for MAiD	Transient drowsiness and vivid dreams	
		60	Female	Ovarian cancer			Subjective "a lot better," improved guilt and self-esteem, withdrew request for MAiD	Transient drowsiness and dizziness	
		80	Male	Prostate cancer			Subjective improvement of depression, improved sleep Received MAiD	Transient drowsiness and confusion	

CGI = Clinical Global Impression; IM = intramuscular; MAiD = medical assistance in dying; PHQ-4 = Patient Health Questionnaire; SC = subcutaneous.

Table 4 Summary of findings from quasi-experimental studies

Authors	Design	n	Palliative care diagnosis	Intervention (dose, route, duration)	Control	Main outcomes	Secondary outcomes	Depression measures	Results (depression)	Side effects
Falk[58]	Observational, retrospective chart review	16 (eight intervention, eight control)	Inpatient/ palliative care unit; cancer (various)	Single dose of 0.25 mg/kg IV S-ketamine	Standard care (does not require ketamine for pain)	Anxiety	Depression	STADI score before and 1-4 days after treatment	No significant effect of S-ketamine on depression, compared with control ($F_{1,14}$ = 0.31, p = 0.59) and baseline ($F_{1,14}$ = 1.80, p = 0.20)	No serious side effects, changes in restlessness/anxiety or persistent psychotomimetic effects
Irwin[16]	Open label trial	14 (intervention)	Hospice; multiple (cancer and non-cancer)	Daily oral doses of 0.5 mg/kg ketamine for 28 days	None	Depression	Anxiety	HADS score at baseline and days 3, 7, 14, 21, and 28	HADS-D scores on days 14 (mean = 3.5, 95%CI 1.09-5.90, p = 0.01), 21 (mean = 4.1, 95%CI 2.0-6.2, p = 0.002), and 28 (mean = 4, 95%CI 2.3-5.9, p = 0.001) were significantly lower than the baseline scores	No vital sign changes or serious side effects Mild side effects (diarrhea, trouble sleeping, and trouble sitting) were observed in 12.5% of the patients

HADS = Hospital Anxiety and Depression Rating Scale; IV = intravenous; STADI = State Trait Anxiety Depression Inventory.

Inventory (STADI)[57] score for depression (esketamine vs. control: $F_{1,14}$ = 0.31, p = 0.59, 1-4 post-injection days vs. baseline: $F_{1,14}$ = 1.80, p = 0.20). There was no evidence of a persistent psychotomimetic effect of esketamine.[58]

Irwin et al.[16] conducted an open-label trial of 14 hospice patients with various chronic conditions eligible for palliative care who received daily oral ketamine doses for 28 days (up to 0.5 mg/kg per dose). Four participants withdrew from the study after 14 days due to no improvement, and two withdrew due to complications unrelated to ketamine treatment. The remaining patients showed $\geqslant$ 30% improvement in the HADS-D score. Among the six patients who withdrew, none showed improved HADS-D scores. Post-hoc analyses revealed significantly lower HADS-D scores on day 14 (mean D = 3.5, d = 1.14, 95%CI 1.09-5.90, p = 0.01), day 21 (mean D = 4.1, d = 1.364, 95%CI 2.0-6.2, p = 0.002), and day 28 (mean D = 4, d = 1.34, 95%CI 2.3-5.9, p = 0.001) compared with the baseline scores. There were no changes in vital signs or serious adverse events. Mild symptoms, including diarrhea and trouble sleeping, occurred in 12.5% of the patients.

Among these quasi-experimental studies, Irwin et al.[16] reported sustained improvement for 28 days, whereas Falk et al.[58] reported negative results. Notably, Falk et al.[58] used a lower IV ketamine dose than most of the other studies,[59] which might have affected the efficacy of the drug. Furthermore, the control group comprised patients who were not prescribed ketamine because they did not have uncontrolled pain and showed a trend toward lower depression scores, which indicates a better mood due to more adequate pain control. Additionally, the study reported five deaths in the ketamine group and one death in the placebo group, which indicates better overall health in the control group.

Randomized controlled trials (RCTs)

We included seven RCTs on 1,125 participants. Most studies were conducted in the perioperative setting of tumor resection surgery.

Salas et al.[26] conducted a randomized, double-blind, placebo-controlled trial on 20 patients in palliative care units. The patients had locally advanced or metastatic cancer and pain refractory to opioids. The main objective was assessing pain control; however, depressive symptoms were included as a secondary objective. Eleven patients (active group) received a single 48-h infusion of IV ketamine, which was titrated from 0.5 mg/kg per day for the first 24 h to 1 mg/kg per day for the next 24 h.

The Edmonton Symptom Assessment Scale (ESAS)[60] was used to assess depressive symptoms at baseline (T0), 2 h (T1), 24 h (T2), and 48 h (T3). There were no differences in the ESAS subscale scores at T2 and T3 compared with the baseline scores (T2: ketamine = 0.27-2.41, placebo = -1.13-2.53, p = 0.13; T3: ketamine = 0.60-0.43, placebo = -2.38-3.50, p = 0.08). There were no adverse effects related to ketamine administration.

Wang et al.[27] reported the use of ketamine to treat depression after laparoscopic total hysterectomy. They included 417 women with cervical carcinoma and mild/

moderate depression (HAM-D score: 8-24) who underwent hysterectomy and were randomized to receive 0.5 mg/kg IV racemic ketamine (104 patients), 0.5 mg/kg (high-dose) S-ketamine (104 patients), 0.25 mg/kg (low-dose) S-ketamine (104 patients), or placebo (50 mL normal saline, 105 patients). A single ketamine infusion was administered after 1 h of analgesia.

Depression was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17)[61] at 1, 2, 3, 5, and 7 postoperative days. All treatment groups showed lower HAMD-17 scores at 1, 2, and 3 days than the control group (p < 0.05). The high-dose S-ketamine (0.5 mg/kg) group had the lowest HAMD-17 score (p < 0.05). There was no among-group difference at 5 postoperative days in HAMD-17, operative time, bleeding, or hospitalization time, nor in the 1-month complication rate (nausea, dizziness, and vomiting).

Fan et al.[28] conducted an RCT including 37 patients with newly diagnosed cancer. The patients were randomized to receive a single infusion of placebo (0.05 mg/kg midazolam) or IV 0.5 mg/kg racemic ketamine). After 7 days, they were assessed for depression, using the MADRS, and for suicidal ideation, using the Beck Scale for Suicidal Ideation (BSI)[62] and the corresponding subscale of the MADRS (MADRS-SI).

Ketamine treatment showed antidepressant effects on day 1 (24.46±8.04 vs. 31.89±7.39, p = 0.0339) and day 3 (25.09±7.07 vs. 32.03±7.21, p = 0.0546); however, this effect was not significant on day 7. Additionally, the BSI and MADRS-SI scores were significantly decreased in the ketamine group on day 1 (BSI, p = 0.0474; MADRS-SI, p = 0.0119) and day 3 (BSI, p = 0.0265; p = 0.0107). There were no significant adverse psychiatric symptoms during the follow-up period.

Xu[29] conducted an RCT on 50 women who underwent modified radical mastectomy for unilateral breast cancer and were randomized to receive intraoperative infusions of 0.5 mg/kg ketamine IV or isotonic saline for depression (HAMD-17 score ⩾ 17). The HAMD-17 scores were significantly lower in the ketamine group at day 1 (12.55±4.50 vs. 18.64±3.83, p < 0.05) and day 3 (10.64±4.33 vs. 16.27±4.45, p < 0.05), but not at day 7 after operation (13.45±5.21 vs 17.36±6.25, p>0.05). Moreover, the HAMD-17 scores in the ketamine group were lower (p < 0.05) on days 1, 3, and 7 than the baseline scores.

There were reports of nausea, irritability, and mild respiratory depression, with no significant between-group difference in the incidence of adverse reactions. Compared with the control group, the ketamine group had a non-significantly longer duration of extubation (p > 0.05).

An RCT conducted by Fallon[30] reported the effect of oral ketamine for neuropathic pain in patients with cancer, with depressive symptoms being a secondary measure. They randomized 214 patients to receive placebo or a daily dose of oral ketamine (titrated from 40 mg to 400 mg daily for 2 weeks and then maintained for 16 days). There was no between-group difference in HADS-D score improvement (ketamine = -3.481, placebo = -3.654, median difference = 0.173 [-0.500 to 0.958]). There were eight and 10 adverse events (cognitive disturbance,

dizziness, fatigue, nausea, and somnolence) in the ketamine and placebo groups, respectively.

An RCT conducted by Liu[31] reported on 303 women with breast cancer who underwent modified radical mastectomy and were randomized to receive an IV injection of 0.125 mg/kg racemic ketamine (n=102), 0.125 mg/kg of S-ketamine (n=101), or placebo (normal saline, n=100) for mild/moderate depression (HAMD-17 score = 8-24). They underwent follow-up assessment using the HAMD-17 for 3 months.

Compared with the placebo group, both ketamine groups showed significantly lower HAMD-17 scores at 3 days (S-ketamine = 11.4±2.2; racemic ketamine = 13.2±2.5; placebo = 16.4±2.0, p < 0.001), 1 week (S-ketamine = 9.4±3.0; racemic ketamine = 10.5±2.9; placebo = 11.2±3.6, p < 0.001) and 1 month (S-ketamine = 6.9±2.8; racemic ketamine = 9.5±2.9; placebo = 11.0±3.8, p < 0.001) after surgery. Further, the S-ketamine group showed lower scores than the racemic ketamine group (p < 0.05). At 3 months postoperatively, there were no significant among-group differences in HAMD-17 scores (S-ketamine = 6.5±3.3; racemic ketamine = 7.5±3.2; placebo = 7.5±3.0, p = 0.050). There were no significant among-group differences in mean operative time (p = 0.562); mean bleeding volume (p = 0.556); and nausea, dizziness, or vomiting (p = 0.986).

An RCT conducted by Zhou[32] reported on 84 patients undergoing elective surgical resection of supratentorial brain tumors who had moderate/severe depression (Patient Health Questionnaire 9[63] [PHQ-9] score ⩾ 10 and MADRS score ⩾ 22) and received a single intraoperative infusion of 0.5 mg/kg IV ketamine (n=41) or placebo (normal saline, n=43). Patients were assessed on days 1 and 3 as well as at discharge. Compared with the placebo group, the ketamine group showed a higher treatment response rate on day 3 (41.5 vs. 16.3%, relative risk [RR]: 2.25, 95%CI 1.18-5.50) and remission rate on discharge (29.3 vs. 7.0%; RR: 4.20, 95%CI 1.28-13.80). Further, compared with the placebo group, the ketamine group showed nonsignificantly lower postoperative depressive scores. There were no significant between-group differences in the number of patients with manic, psychotic, or dissociative symptoms, nor in delirium, prolonged hospital stay, or blood loss.

Among the seven included RCTs, two reported negative results. These two RCTs[26,30] used pain control and depressive symptoms as the primary and secondary objectives, respectively. Accordingly, there were no specified cutoff values for minimum depression severity, and the samples might have included individuals without depression as well as those with severe depression, which might have resulted in weaker findings regarding efficacy. This is consistent with the findings of a large negative RCT conducted by Mashour et al.,[64] which we did not include due to incompatible outcomes. Its primary objective was to use intraoperative ketamine to prevent depressive symptoms after major surgeries. They included 670 patients aged ⩾ 60 years who underwent cardiac and non-cardiac surgeries and were randomized to receive 1 mg/kg IV ketamine (high dose, 223 patients),

0.5 mg/kg (low dose, 226 patients), or saline placebo (221 patients). There was no significant among-group difference in the severity of depressive symptoms on days 3 (p = 0.773) and 30 (p = 0.271) after surgery.

The limited efficacy of ketamine as a preventive intervention could have contributed to the negative results of the two aforementioned studies. The patients with depression may have responded to the intervention; however, euthymic individuals may also develop mood disorders, which counterbalances the effect.

Four studies described the perioperative use of ketamine in patients with clinically significant depressive symptoms,[27,29,31,32] which reported an overall positive effect that lasted for 5-30 days. Among them, two compared the use of *S*-ketamine and *R/S*-ketamine, with *S*-ketamine showing a more robust effect in both studies.[27,31] Moreover, Wang et al.[27] described that the 0.5 mg/kg dose had higher efficacy than the 0.25 mg/kg dose. This is consistent with the previously reported higher potency of *S*-ketamine, owing to its higher affinity for NMDA receptors.[65]

Fan et al.[28] demonstrated the treatment efficacy of ketamine against depressive symptoms (more specifically, against suicidal ideation). Compared with placebo, ketamine showed a positive effect that started at day 1 and was sustained for at least 3 days. Additionally, ketamine showed a fast-acting effect on suicidal ideation,[66] which is highly beneficial for specific populations. Given the inherent urgency in palliative care as well as the urgency required for controlling suicidal behavior, ketamine is a potential game-changer.

Gray literature

We report data available for three unpublished clinical trials. An RCT conducted by Bright[67] (https://clinicaltrials.gov/ct2/show/study/NCT01680172) recruited five patients with cancer who received a single oral dose of 0.5 mg/kg ketamine solution or placebo for depression (HADS-D score > 11). The mean (SD) HADS-D score for the ketamine group (n=3) was 12.7 (1.5) at baseline and 11.7 (2.3) at 120 min, while the corresponding values in the placebo group (n=2) were 14.5 (2.1) and 10.5 (3.5), respectively. All participants had minor side effects (e.g., rapid heart rate, vomiting, headache, drowsiness, and shortness of breath).

An open-label trial conducted by Singh[68] (https://clinicaltrials.gov/ct2/show/results/NCT03146806) enrolled 10 patients who received ketamine for uncontrolled cancer pain and depression, using the MADRS score as a secondary outcome. The patients were followed for five visits at 2-to-5-day intervals. On the first visit, the patients received 10 mg intranasal ketamine, with the MADRS scores (SD) being 18.7 (6.57) at baseline and 13.5 (4.38) at 180 min. On the second visit, they received 10 mg IV ketamine, with the MADRS scores (SD) being 13.4 (6.40) at baseline and 13.3 (5.31) at 180 min. On the third visit, they received 30 mg intranasal ketamine, with the MADRS scores (SD) being 12 (5.05) at baseline and 11.3 (6.15) at 180 min. On the fourth visit, they received 50 mg intranasal ketamine, with the MADRS scores (SD)

being 11.89 (8.34) at baseline and 9.67 (8.34) at 180 min. The fifth visit served only as a follow-up, with the MADRS scores being 14.78 (7.31).

Rodríguez-Mayoral[69] conducted an RCT (https://clinicaltrials.gov/ct2/show/study/NCT04471818) on eight patients with cancer who were randomized to receive 0.5 mg/kg IV ketamine (n=4) or placebo (n=4) for depression. Weekly injections were administered for 4 weeks, with assessment using the Brief Edinburgh Depression Scale (BEDS).[70] The ketamine group had lower BEDS scores than the placebo group at 3 weeks post-intervention (3.0 [SD: 2.160] vs. 11.75 [SD: 3.594]; p = 0.006). The most common adverse events were drowsiness and nausea; there were no serious adverse events.

Among these unpublished studies, Rodriguez-Mayoral[69] reported a robust response to weekly IV ketamine. Similarly, the remaining unpublished data demonstrated a progressive decrease in symptom severity after repeated ketamine dosing.

Discussion

Across all the included studies, the most consistent finding was safety. There were no reports of serious adverse effects leading to treatment discontinuation. The most common adverse effects were dissociative symptoms, nausea, vomiting, dizziness, somnolence, and confusion, with most RCTs reporting similar rates between the active and placebo groups. Further, studies that used ketamine in perioperative settings did not report differences in complication rates, including operative time, blood loss, and length of hospital stay.[27,29-31] Hypertension and hemodynamic instability, which are common concerns regarding the use of ketamine,[71] were not limiting factors in the reported studies. One case report described a long follow-up period with 10 months of repeated doses and a progressive improvement in tolerability.[42]

Our study selection approach allowed analysis of a large spectrum of palliative-care patients with low or high life expectancies, as well as patients with cancer and non-cancer diagnoses. Ketamine appeared to be safe even among patients with very poor prognoses; however, treatment was frequently interrupted due to complications of the primary disease. These tolerability findings could inform the widespread use of ketamine for depression in palliative care settings, since its use in this scenario is mainly impeded by the lack of safety data.

Regarding efficacy, most case reports described a large positive effect, with an early onset of action from as early as 1 h to approximately 48 h. Maintenance of effect was variable, with only a few participants showing sustained remission after a single ketamine dose.[35] However, most patients relapsed after 1-7 days and required follow-up doses, with some patients not responding. The routes of administration, dosing regimen, and reported follow-up measures varied widely.

Nonetheless, numerous aspects regarding ketamine treatment within palliative care remain unclear. As mentioned above, only one small-scale RCT has focused on patients with depression outside the perioperative

Table 5 Summary of findings from RCTs

Authors	n	Setting and palliative care diagnosis	Intervention (dose, route, duration)	Control	Main outcomes	Secondary outcomes	Depression measures	Results (depression)	Side effects
Salas[26]	20 (11 intervention, nine control)	Palliative care unit; locally advanced or metastatic cancer and pain refractory to opioids	A single continuous 48-h IV infusion of morphine + ketamine (0.5-1.0 mg/kg)	A single continuous 48-h IV infusion of morphine + placebo (not described)	Pain	Depression, tiredness, nausea, anxiety, drowsiness, lack of appetite, well-being, shortness of breath, sedation, satisfaction	ESAS score at baseline (T0), 2 h (T1), 24 h (T2), and 48 h (T3)	No differences were found (T2: ketamine = 0.27-2.41 placebo = -1.13-2.53 p = 0.13; T3: ketamine = 0.60-1.43 placebo = -2.38-3.50 p = 0.08)	One patient died in the placebo group No ketamine-related adverse effects
Wang[27]	417 (313 intervention, 104 control)	Hospital; women with cervical carcinoma undergoing laparoscopic total hysterectomy	A single IV injection 1 h after analgesia of 0.5 mg/kg R/S-ketamine (n=104), 0.5 mg/kg S-ketamine (n=104); or 0.25 mg/kg S-ketamine (n=104)	A single IV injection 1 h after analgesia of 50 mL normal saline (104 patients)	Depression, pain	None	HAMD-17 score at baseline and days 1, 2, 5, and 7	In all treatment groups, the HAMD-17 scores were lower at 1, 2, and 3 days than in the control group (p < 0.05)The high-dose S-ketamine (0.5 mg/kg) group had the lowest HAMD-17 scores (p < 0.05) No difference at 5 postoperative days	No difference in operative time, bleeding, length of hospital stay, or 1-month complication rate (nausea, dizziness, vomiting)
Fan[28]	37 (20 intervention, 17 control)	Hospital; newly diagnosed cancer (various)	A single 40-min IV infusion of 0.5 mg/kg IV R/S-ketamine	A single 40-min IV infusion of 0.05 mg/kg midazolam	Suicidal ideation	Depression	MADRS score at baseline and days 1, 3, and 7	The ketamine group was less depressed on days 1 (MADRS = 24.46±8.04 vs. 31.89±7.39, p = 0.0339) and 3 (25.09±7.07 vs. 32.03±7.21, p = 0.0546) No difference on day 7	No increase in emergent psychiatric symptoms
Xu[29]	50 (25 intervention, 25 control)	Hospital; female patients undergoing modified radical mastectomy of unilateral breast cancer	A single 10-min IV infusion of 0.5 mg/kg ketamine 1 h after the start of anesthesia	A single 10-min IV infusion of isotonic saline 1 h after the start of anesthesia	Depression	Pain	HAMD-17 score at baseline as well as days 1, 3 and 7	The ketamine group had significantly lower HAMD-17 scores than the control group at 1 and 3 postoperative days (p < 0.05) At postoperative day 7, there was no significant between-group difference (p > 0.05)	No between-group difference in the incidence of adverse reactions The ketamine group had one case of nausea, two cases of irritability, and one case of mild respiratory depression
Fallon[30]	214 (107 intervention, 107 control)	Unspecified setting; cancer-related neuropathic pain	Daily doses of 40-400 mg oral ketamine (2-week titration followed by fixed dose for 16 days)	Placebo (not described)	Pain	Depression, anxiety	HADS score (time points not specified)	No between-group difference Mean HADS (ketamine) = -3.481; mean HADS (placebo) = -3.654; median difference = 0.173 (-0.500 to 0.958)	Eight and 10 adverse events in the ketamine and placebo groups, respectively (cognitive disturbance, dizziness, fatigue, nausea, somnolence)

Table 5. (*continued*)

Authors	n	Setting and palliative care diagnosis	Intervention (dose, route, duration)	Control	Main outcomes	Secondary outcomes	Depression measures	Results (depression)	Side effects
Liu[31]	303 (203 intervention, 100 control)	Hospital; female breast cancer patients who received modified radical mastectomy	A single IV infusion of 0.125 mg/kg of *R/S*-ketamine (n=102); or 0.125 mg/kg of *S*-ketamine (n=101)	A single IV infusion of normal saline (n=100)	Depression	Pain	HAMD-17 at baseline and days 3, 7, 30 and 90	HAMD-17 scores were lower at three days, 1 week, and 1 month after surgery in both ketamine groups when compared to the control group Scores in the *S*-ketamine group were lower than in the *R/S*-ketamine group (p < 0.05)No difference at 3 months	No side effects are reported
Zhou[32]	84 (41 intervention, 43 control)	Hospital; patients undergoing elective surgical resection of supratentorial brain tumor	A single 40-min IV infusion of 0.5 mg/kg ketamine	A single 40-min IV infusion of normal saline	Depression	Anxiety, delirium, pain	PHQ-9 and MADRS scores at baseline; days 1, 2, and 3; and at discharge.	The ketamine group had a higher proportion of patients with treatment response on day 3 than the placebo group (41.5 vs 16.3%, respectively; RR: 2.25, 95%CI 1.18-5.50) The rate of remission on discharge was higher with ketamine than with placebo (29.3 vs. 7.0%; RR: 4.20, 95%CI 1.28-13.80)	Three days after surgery, there was no significant between-group difference in the number of patients who experienced manic symptoms (4.9 vs. 2.3%), psychotic symptoms (7.3 vs. 9.3%), or dissociative symptoms (7.3 vs. 2.3%)

ESAS = Edmonton Symptom Assessment Scale; HADS = Hospital Anxiety and Depression Rating Scale; HAMD-17 = Hamilton Depression Rating Scale; IV = intravenous; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; RCT = randomized clinical trials; RR = relative risk.

context,[28] with only a few other small-scale unpublished clinical trials. Conversely, the two other available studies not conducted in a surgical context primarily focused on pain and reported mixed results.

A 2017 Cochrane review[72] included three studies on the use of ketamine for cancer pain, with various regimens (intrathecal ketamine, IV bolus ketamine, and SC ketamine); the largest study used SC ketamine.[73] The intervention was generally safe, but prominent psychomimetic effects were reported more frequently in the ketamine group. Other minor side effects, such as drowsiness, nausea, hallucinations, cognitive disturbance, and injection site reaction, as well as two major adverse reactions (bradyarrhythmia and cardiac arrest), were also reported. Therefore, safety evidence in this area remains scarce, and efficacy for the treatment of pain was extrapolated from trials of acute perioperative pain.

Furthermore, data regarding route of administration are highly heterogeneous. Findings with the SC route from pain studies cannot be extrapolated for the treatment of depressive symptoms, where most utilize IV or oral administration (Table 5). Even more scarce are studies that used an intranasal route of administration, which is the only label-approved route for the treatment of depression. Although robust data are emerging on the comparison of ketamine enantiomers for depression in the general population,[74] there is very little information on the preferred route.

Apart from psychomimetic, neurological, and gastrointestinal adverse effects, there are other concerns regarding the use of ketamine in complex patients. Through catecholamine release and reuptake blockade, ketamine can increase blood pressure and pose a risk to patients with coronary artery disease and hypertension. Other rare adverse effects are laryngospasm and apnea.[75] Subsequently, there are specific concerns for the use of ketamine in oncologic patients. Some of the mechanisms of action hypothesized to contribute to the antidepressant effect of ketamine are the activation of neuroplasticity-related signaling pathways such as brain-derived neurotrophic factor and mechanistic target of rapamycin (mTOR) complex 1, which promote protein synthesis.[76] This same mechanism is implicated in tumor growth, and activating mutations of mTOR have been linked to multiple cancer types, whereas mTOR inhibitors have been used for cancer treatment.[77]

However, these concerns are not strongly supported by evidence, as there are no studies describing progression of malignancy that may be attributed to ketamine use. Furthermore, in vitro studies also suggest a reduction of mTOR activity in ketamine-treated cells, resulting in increased apoptosis of tumoral cells. This finding was also replicated in an animal model, which showed a reduction in tumor volume.[78] Finally, a point can be made that even if the use of ketamine for the treatment of depression results in accelerated tumor growth, the benefits may still outweigh the risks in patients with very short prognoses.

Currently, ketamine can be considered for the treatment of depression in patients with cancer receiving palliative care who are undergoing tumor resection under general anesthesia. In this setting, ketamine could be a safe and effective option for rapid symptom relief. Based on the available evidence, the preferred regimen would be a single IV infusion of 0.5 mg/kg S-ketamine after anesthesia induction.

Evidence to support the efficacy of ketamine in non-surgical patients receiving palliative care is now mainly derived from case reports and open-label studies. Therefore, we cannot draw specific conclusions for daily clinical use. Nevertheless, the safety data are reassuring; additionally, there is a need for large-scale RCTs aimed at depressive symptom relief within various palliative care populations.

Finally, our findings indicate that ketamine is not appropriate as a preventive measure for depressive symptoms in patients without depression receiving palliative care.

In conclusion, ketamine is a potential therapeutic option for depression treatment in palliative care settings. It appears to be safe, well-tolerated, and effective for perioperative depression. The remaining evidence is still conflicting; however, case reports and open-label studies have provided promising results. Future studies should focus on non-surgical and non-cancer palliative care populations and seek to determine the optimal therapeutic regimen.

Acknowledgements

Disclosure

The authors report no conflicts of interest.

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