

ORIGINAL RESEARCH

Subanesthetic Ketamine for Opioid-Refractory Cancer Pain: Efficacy, Safety, and Opioid-Sparing Effects

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ABSTRACT

Background: Opioid-refractory cancer pain is a major clinical challenge, affecting an estimated 20–40% of patients despite optimized opioid therapy. Subanesthetic-dose ketamine, an NMDA receptor antagonist, has emerged as a potential adjunct for managing such pain.

Methods: A scoping review was conducted through April 2025 in PubMed, ScienceDirect, SpringerLink, and the Cochrane Library. Included studies involved cancer patients with opioid-refractory pain treated with subanesthetic ketamine. One RCT, one cohort study, and eight case reports were analyzed. Outcomes included pain relief, opioid dose reduction, and adverse effects.

Results: Ten studies met inclusion criteria. Subanesthetic ketamine provided rapid pain relief in most cases, with pain scores decreasing by 37–100% within 1–2 days. All eight case reports demonstrated clinically meaningful reductions in pain intensity, with opioid-sparing effects reported across all cases. Daily opioid dose reductions ranged from 46% to 99%, with several cases reporting over 90% reduction in oral morphine equivalents. The RCT showed a non-significant trend toward improved pain outcomes, likely due to small sample size and limited power. Adverse effects were generally mild (e.g., hallucinations, sedation), with rare serious events. Ketamine was overall well tolerated across case reports, the RCT, and the cohort study.

Conclusions: Subanesthetic ketamine is a promising adjunct for opioid-refractory cancer pain, offering effective analgesia and substantial opioid reduction potential. Its safety profile is acceptable under careful monitoring. However, heterogeneity among studies and the limited high-quality evidence emphasize the need for larger, well-designed trials to establish optimized dosing, long-term safety, and standardized clinical guidelines.

Keywords: Adjunct Therapy; Cancer Pain; Ketamine Infusion; Opioid-Refractory Pain; Subanesthetic Ketamine.

INTRODUCTION

Cancer-related pain remains one of the most prevalent and distressing symptoms experienced by patients, particularly in advanced or terminal stages of the disease¹⁻³. Epidemiological studies consistently report that approximately 66% of patients with metastatic cancer experience some form of pain, with up to 40% describing it as moderate to severe in intensity^{4,5}. The World Health Organization's analgesic ladder has established opioids as the cornerstone of cancer pain management, often in combination with co-analgesics^{6,7}. While this approach provides effective relief for the majority, a portion of patients require more advanced strategies when conventional therapies are insufficient^{4,8,9}.

Despite appropriate opioid use and dose escalation, an estimated 20-40% of cancer patients suffer from opioid-refractory pain, defined as inadequate pain control or unacceptable side effects despite optimized treatment^{6,10-12}. This phenomenon may result from opioid tolerance, disease progression, or the presence of complex pain syndromes such as neuropathic or incident pain^{13,14}. A study by Bennett et al. (2019) highlighted that neuropathic

pain mechanisms are present in up to 40% of cancer patients, and this subgroup is significantly more likely to experience poor response to opioids¹⁵. Additionally, central sensitization and NMDA receptor activation have been implicated in the development of opioid tolerance and hyperalgesia, contributing to the refractory nature of the pain^{12,14}. Factors such as younger age, high opioid requirements, psychological comorbidities, and a history of substance misuse have also been associated with poorer pain outcomes^{7,9,13}. Given these challenges, there is a growing interest in advanced strategies for managing opioid-refractory pain when conventional therapies prove insufficient^{9,16,17}. Options such as cannabinoids, botulinum toxin A, and capsaicin have been explored, though their use is often limited by inconsistent evidence and variable patient response^{14,18,19}. Among these, subanesthetic ketamine has emerged as a particularly promising adjunct due to its potential to enhance analgesia in difficult-to-treat cases and improve patient outcomes when added to opioid regimens^{10,11,13,20}.

Ketamine, a dissociative anesthetic and N-methyl-D-aspartate

(NMDA) receptor antagonist, has emerged as a promising option for managing opioid-refractory cancer pain¹⁰. At subanesthetic doses, it provides analgesia by modulating central sensitization and reducing opioid-induced hyperalgesia, without causing the deep sedation or psychotomimetic effects associated with higher doses^{21,22}. Administered intravenously or subcutaneously, subanesthetic ketamine has demonstrated the potential to enhance pain control and decrease opioid requirements^{23,24}. In a case report by Amin et al. (2014), a patient with metastatic breast cancer experienced a 37% reduction in pain scores and a 61.4% decrease in opioid use after transitioning from intravenous to oral ketamine. Institutions such as the University of California San Diego Health System have incorporated ketamine infusions into standard care for refractory pain¹⁸. These findings highlight ketamine's growing role as an adjuvant in the multimodal management of cancer pain and emphasize the need for further research to optimize and standardize its clinical use²⁵⁻²⁷.

Currently, the most comprehensive systematic review of subanesthetic ketamine for cancer pain

includes randomized trials evaluating its use both alone and as an adjunct to opioids²⁸. However, the evidence remains limited for its application specifically in opioid-refractory cancer pain, a population in which ketamine is often considered due to its NMDA receptor-mediated opioid-sparing potential²². This highlights a critical gap in targeted clinical evidence for this high-need population. To address this, the current review examines the therapeutic role of subanesthetic ketamine as an adjunct to managing opioid-refractory cancer pain. The primary outcomes include reductions in reported pain scores and the potential for opioid dose minimization, quantified in oral morphine equivalents, while preserving adequate analgesia. Secondary outcomes assess the agent's safety and tolerability, with particular attention to the frequency and clinical severity of adverse events.

Methods

Study Design and Registration

This scoping review was conducted under the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to evaluate the efficacy and safety of subanesthetic ketamine,

administered as an adjuvant therapy, for opioid-refractory cancer pain in adult and pediatric populations. The review protocol was developed based on PICOS criteria and focused on qualitative and quantitative outcomes related to pain relief, treatment effectiveness, and adverse effects.

Eligibility Criteria

- Population: Adults (18-65 years) or children (0-18 years) with cancer-related pain unresponsive to opioid therapy.
- Intervention: Subanesthetic-dose ketamine administered via intravenous, subcutaneous, or oral routes. Accepted dosing includes bolus (≤ 0.5 mg/kg), continuous infusion (≤ 1 mg/kg/hour), or oral dosing within clinically accepted subanesthetic ranges (e.g., ≤ 3 mg/kg per dose or ≤ 6 mg/kg/day), used as an adjunct to standard analgesic regimens.
- Comparison: Placebo, standard care, or other non-ketamine interventions, when available.
- Outcomes:
 - Primary Outcomes: Pain reduction or relief, measured using validated pain scales (e.g., VAS, NRS).
 - Secondary Outcomes: Treatment tolerability, adverse effects (e.g., hallucinations, sedation, nausea, cardiovascular changes), and opioid dose

reduction, expressed in oral morphine equivalents (OME).

- Study Design: Randomized controlled trials (RCTs), non-randomized trials, observational studies, case series, and case reports.
- Language: Articles published in English.
- Availability: Full-text accessible.

Exclusion Criteria

- Population: Studies involving non-cancer pain, healthy volunteers, or animal/in vitro models.
- Intervention: Studies administering ketamine at anesthetic or supratherapeutic doses, or using ketamine as monotherapy without concurrent opioid treatment.
- Study Types: Editorials, conference abstracts, narrative reviews, meta-analyses, and expert commentaries.

Search Strategy

A comprehensive literature search was conducted across the following databases: PubMed, ScienceDirect, SpringerLink, and Cochrane Library from inception until April 2025. The following search terms were used: ("Ketamine" OR "Low-dose ketamine" OR "Subanesthetic ketamine") AND ("Opioid" OR "Opioid-refractory" OR "Opioid-resistant") AND ("Cancer Pain" OR "Cancer" OR "Oncology").

Boolean operators and filters were adjusted according to the indexing of each database. Reference lists of relevant articles were also manually screened for additional eligible studies.

Risk of Bias Assessment

The JBI Critical Appraisal Tool was used to assess the quality and risk of bias in the included studies. Depending on study design, appropriate checklists were applied for: Randomized Controlled Trials, Observational Studies, Case Series, and Case Reports. The assessment considered participant selection, exposure measurement, confounding variables, outcome assessment, and completeness of follow-up. Studies were classified as low, moderate, or high risk of bias.

Data Synthesis and Statistical Analysis :

A qualitative descriptive synthesis was performed to summarize key findings across studies. Where available, quantitative data on pain scores and opioid consumption were extracted and compared. A meta-analysis was considered if sufficient homogeneity in outcome measures and study design was observed. In the absence of pooled data, a narrative

synthesis was conducted, focusing on efficacy, safety, and tolerability outcomes of subanesthetic ketamine in opioid-refractory cancer pain.

RESULTS

3.1 Study selection and identification

A comprehensive literature search identified a total of 566 records through database searching, including PubMed (n = 257), ScienceDirect (n = 222), SpringerLink (n = 59), and the Cochrane Library (n = 28). After removing duplicates, 518 unique records remained for screening. Title and abstract screening was performed on 97 records, with 421 excluded for not meeting the inclusion criteria. A total of 21 full-text articles were assessed for eligibility. Of these, 11 were excluded due to reasons such as not addressing the outcome of interest (n = 53), being non-English literature (n = 11), or having unavailable full texts (n = 12). After further evaluation, 11 studies were excluded due to inadequate data. Ultimately, 10 studies were included in the final quantitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

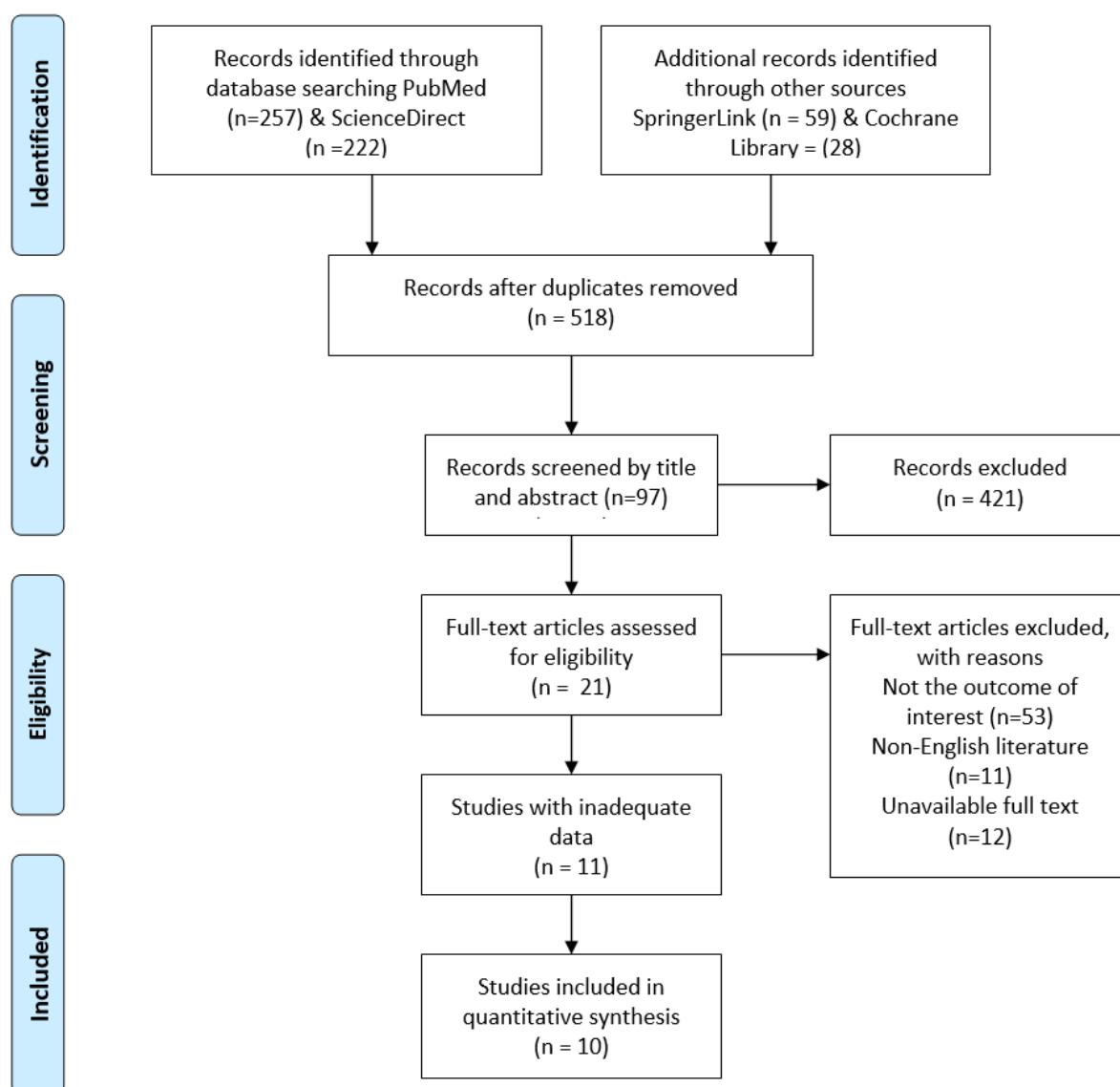


Figure 1. PRISMA Flowchart

3.2 Risk of Bias Assessment

Risk of bias was assessed using the JBI Critical Appraisal Tools for Cohort Studies, Randomized Controlled Trials (RCTs), and Case Reports. The single RCT included Hardy et al., 2012 was rated as low risk of bias, with a score of 11/13 (Table 3)²⁹. One cohort study from Cheung et al., 2020 was included

and rated as having a moderate risk of bias, scoring 7/11 (Table 4)¹⁰. All eight case reports were assessed as having a low risk of bias. Amin et al. 2014, Nath et al. 2022, Waldfogel et al. 2016, Grande et al. 2008, and Nishiyama, 2017 each received a full score of 8 out of 8^{12,18,25,30,31}. Forth et al. 2022, Fine 1999, and Ugur et al. 2009 scored slightly

lower, with 7 out of 8 points (Table 5)^{8,32,33}. Overall, despite the predominance of case reports in the included studies, the risk of bias was generally low, and the methodological quality was considered adequate to support the findings of this review.

3.3 Characteristics of Studies

Ten studies published between 1999 and 2022 were reviewed, including eight case reports, one randomized controlled trial (RCT), and one retrospective cohort study (Table 1)^{8,10,12,18,25,29–33}. The case reports involved nine individual patients aged 4 to 52 years (five males, four females) with advanced or metastatic malignancies, gastric adenocarcinoma, breast cancer, endometrial cancer, pancreatic neuroendocrine tumor, liposarcoma, lymphoma, neuroectodermal tumor, cervical cancer, and abdominal undifferentiated sarcoma (Table 2)^{8,12,18,25,30–33}. All patients presented with opioid-refractory cancer pain, with baseline opioid doses ranging from 16 mg/day in pediatric patients to over 168,000 mg/day oral morphine equivalent (OME) in complex adult cases^{32,33}. The opioids used included morphine, fentanyl, methadone, hydromorphone, and oxycodone,

administered via oral, intravenous continuous infusion, bolus, or patient-controlled analgesia^{8,12,18,25,30–33}.

Ketamine was predominantly administered intravenously in the case reports, with initial bolus doses ranging from 5 to 25 mg or 0.2–0.3 mg/kg, followed by continuous subanesthetic infusions ranging from 0.02 to 0.4 mg/kg/hour. One patient received oral ketamine at 3 mg/kg/day (33). Treatment duration in these cases varied from one to fourteen days. Adjunctive analgesics, such as gabapentinoids, duloxetine, paracetamol, corticosteroids, and sedatives, were frequently employed. Opioid administration routes included intravenous infusion, bolus, oral, and patient-controlled analgesia^{8,10,12,18,25,29–33}.

The RCT by Hardy et al. (2012) was conducted across 10 palliative care centers in Australia, enrolling 185 adult inpatients with opioid-refractory chronic cancer pain. Patients received subcutaneous ketamine infusions over 3 to 5 days, starting at 100 mg/day with dose escalation up to 500 mg/day based on pain response and tolerability. Background opioid doses at baseline were a median of approximately 300–410 mg/day OME. Stable opioid doses

were maintained during the trial, with reductions allowed for toxicity or response²⁹

The retrospective cohort study by Cheung et al. (2020) included 70 adult patients with opioid-refractory cancer pain admitted to a hospital in Hong Kong. Most patients were receiving regular opioid therapy, primarily morphine, with a median baseline opioid dose of 425 mg/day OME. Ketamine was administered mainly by subcutaneous infusion, starting at a median dose of 100 mg/day and titrated up to a maximum of 300 mg/day. Treatment duration ranged approximately from 6 to 15 days. Coanalgesics such as gabapentinoids, antidepressants, and benzodiazepines were commonly used¹⁰.

3.4 Analgesic Effectiveness of Subanesthetic Ketamine

Subanesthetic ketamine has shown consistent effectiveness in managing opioid-refractory cancer pain. Across eight case reports, continuous intravenous infusions of ketamine at doses between 0.02–0.4 mg/kg/h led to meaningful pain relief, often within just a few days. Patients typically presented with severe pain (NRS 7–10) despite high-dose opioid therapy^{8,12,18,25,30–33}. Following ketamine administration,

substantial reductions were observed, with pain scores decreasing from 10 to 7 (Forth et al., 2022), 8 to 5 (Amin et al., 2014), and 7.5 to 1 (Nath et al., 2022)^{8,18,25}. In one pediatric case, oral ketamine at 3 mg/kg/day was administered, reducing pain from 8–9 to 0–1 over two weeks³³. These responses suggest that ketamine can rapidly restore pain control, even in patients who have exhausted other pharmacologic options.

Findings from clinical studies further support these results. In a randomized controlled trial by Hardy et al. (2012), subcutaneous ketamine infusions (100–500 mg/day over 3–5 days) were given to patients with advanced cancer receiving high baseline opioid doses (median 300 mg/day in the ketamine group and 410 mg/day in the placebo group). Although the study did not reach statistical significance on its primary endpoint, some patients in the ketamine group reported reductions in pain intensity, particularly at higher titrated doses²⁹.

Further evidence comes from a retrospective cohort study by Cheung et al. (2020), which evaluated 70 patients with refractory cancer pain treated with subcutaneous ketamine (median starting dose 100 mg/day, titrated up to a

maximum of 300 mg/day). Pain scores significantly improved from a mean NRS of 7.0 to 4.0 ($P < 0.001$). A favorable response—defined as a clinically meaningful reduction in pain—was reported in 70% of patients, with 47.1% achieving at least a 50% reduction in NRS. The ketamine infusion was typically administered over a median of 10 days, and adjunctive co-analgesics were frequently used. Overall, these findings highlight the analgesic potential of subanesthetic ketamine in difficult-to-treat cancer pain. Through both direct pain relief and opioid-sparing effects, ketamine offers a valuable adjunctive strategy when conventional analgesics are insufficient¹⁰.

3.5 Opioid-Sparing Effects of Ketamine

A consistent finding across all nine case reports was a significant reduction in opioid requirements following the initiation of subanesthetic ketamine. This opioid-sparing effect was observed in every report and ranged from modest to profound^{8,12,18,25,30–33}. The percentage reduction in daily oral morphine equivalent (OME) varied from approximately 46.6% to as high as 100%^{25,32}. The most dramatic reduction occurred in the case by Fine et al. (1999),

where the patient's OME decreased from 168,000 mg/day to 0, representing a 100% reduction. However, this reduction occurred in the context of terminal care, where ketamine was initiated as a palliative measure and opioids were discontinued concurrently, limiting the ability to attribute the effect solely to ketamine³². Similarly, Grande et al. (2008) reported a decrease from 161,280 mg/day to ~1,485 mg/day (99.1% reduction), and Waldfogel et al. (2016) described a reduction from approximately 50,160 mg/day to ~2,080 mg/day (95.9% reduction)^{12,30}.

Other cases also demonstrated substantial opioid tapering: Nishiyama (2017) reduced from ~210 mg/day to ~60 mg/day (71.4%), Amin et al. (2014) from 1,657 mg/day to 640 mg/day (61.4%), and Ugur et al. (2009) from 16 mg/day to 6 mg/day (62.5%)^{18,31,33}.

In the pediatric patient also described by Fine et al. (1999), the OME declined from 96,000 mg/day to 0, yielding a 50% reduction by author estimation³². The least reduction occurred in the case by Nath et al. (2022), who reported a decrease from 225 mg/day to 120 mg/day (46.6%), while Forth et al. (2022) observed a drop from 5,266 mg/day to 2,600 mg/day

(50.6%)^{8,25}. These reductions typically occurred within 1 to 14 days of ketamine initiation, suggesting a rapid opioid-sparing effect. This is particularly important in patients at high risk of opioid-related adverse effects, tolerance, or opioid-induced hyperalgesia.

This opioid-sparing trend was further supported by data from the randomized controlled trial by Hardy et al. (2012). In this trial, background opioid therapy was maintained at stable doses during the 5-day ketamine infusion period. Although dose reductions were permitted for reasons such as adverse effects or improved pain control, no quantitative data on opioid dose changes were reported. Additionally, the study found no statistically significant difference in analgesic response between the ketamine and placebo groups, which limits the strength of inference regarding opioid-sparing effects. Nevertheless, the trial's design allowed for dose adjustments, and the use of escalating subcutaneous ketamine doses (100–500 mg/day) may suggest a potential, though unproven, opioid-sparing benefit²⁹.

In contrast, the retrospective cohort study by Cheung et al. (2020) provided more direct evidence. Among 70 cancer patients with refractory pain,

the median baseline OME was 425 mg/day. Following continuous subcutaneous ketamine titration, 68.6% of patients experienced a reduction in opioid dosage. Although specific tapering protocols (e.g., 20% daily reductions) were not detailed in the report, opioid reduction was achieved in the majority of patients, supporting ketamine's adjunctive benefit in this setting. These results indicate a clinically meaningful role for ketamine in managing opioid-refractory pain, particularly in populations with high opioid tolerance¹⁰.

3.6 Safety Profile and Tolerability of Ketamine

The safety profile of subanesthetic ketamine was largely favorable across the included studies. In the case reports, ketamine was generally well tolerated, with no serious or life-threatening adverse events directly attributed to its use^{8,12,18,25,30–33}. Mild neuropsychiatric symptoms were observed in a few cases^{8,12,30}. For example, Forth et al. (2022) reported restlessness and mild hallucinations, which were successfully managed with supportive medications⁸. Waldfogel et al. (2016) documented sedation, delirium, and mild hallucinations

that resolved after ketamine discontinuation¹². Most other reports, including those by Amin et al. (2014), Nath et al. (2022), and Ugur et al. (2009), explicitly stated that no adverse effects occurred^{18,25,33}. Notably, in the pediatric patient described by Ugur et al. (2009), oral ketamine was well tolerated without evidence of nausea, sedation, hallucinations, or respiratory depression³³.

In contrast, the randomized controlled trial by Hardy et al. (2012) reported a higher incidence of adverse effects in the ketamine group compared to placebo. The incidence rate ratio was 1.95. Side effects included psychotomimetic symptoms, somnolence, and injection site irritation. Two serious adverse events were recorded, including bradyarrhythmia and cardiac arrest, both considered possibly related to ketamine, although a definitive causal relationship could not be confirmed. These results emphasize the potential for increased adverse events in controlled trial settings with structured monitoring and comprehensive reporting²⁹.

Similarly, the retrospective cohort study by Cheung et al. (2020) found that ketamine was generally well

tolerated. However, mild to moderate adverse effects were reported in some patients. These included drowsiness in 45.7%, hypertension in 34.3%, nightmares in 25.7%, and hallucinations in 12.9% of cases. In several patients, tolerability issues led to treatment modifications. Ketamine was temporarily suspended in 7.1% of patients and permanently discontinued in 4.3% due to intolerable side effects¹⁰.

Although the frequency and severity of adverse events varied across studies, subanesthetic ketamine appeared to be generally safe when used under proper clinical supervision. Most side effects were mild, reversible, and manageable with supportive care. Nonetheless, caution remains necessary, particularly for patients with preexisting cardiovascular conditions or psychiatric vulnerabilities^{8,10,12,18,25,29–33}.

DISCUSSION

Refractory cancer pain refers to persistent pain despite appropriate opioid therapy and is particularly prevalent among patients with advanced or metastatic disease, where the pain is often mixed nociceptive and neuropathic^{9,14}. Up to 20% of patients experience inadequate relief despite escalating opioid doses¹². A major

contributing factor to this phenomenon is opioid-induced hyperalgesia, a state of increased pain sensitivity caused by prolonged opioid use²⁰. This condition is mediated through peripheral and central sensitization involving NMDA receptor activation³⁴. Peripherally, NMDA receptor activation increases nociceptor excitability and neurotransmitter release, while centrally, it amplifies excitatory signaling in the spinal cord, lowers pain thresholds, and disrupts inhibitory pathways^{23,25}. These mechanisms may paradoxically worsen pain with continued opioid use²⁵. Consequently, management strategies include opioid de-escalation and the use of NMDA receptor antagonists to counteract this process²⁵. Clinically meaningful pain control is often defined as a ≥ 2 -point reduction in Brief Pain Inventory (BPI) average pain score, with no more than four breakthrough doses required in 24 hours, a target frequently not achieved in refractory cases²⁹.

Ketamine, a phencyclidine derivative classified as a dissociative anesthetic, has emerged as a valuable adjunct in managing opioid-refractory cancer pain when administered at subanesthetic doses^{28,35}. Its principal mechanism of action is the non-

competitive antagonism of the NMDA receptor, which plays a central role in the development of central sensitization, hyperalgesia, allodynia, and opioid tolerance^{30,35}. Ketamine binds to open NMDA receptor channels and secondary modulatory sites, thereby attenuating calcium influx and downstream excitatory signaling³⁶. This contributes to the reduction of dorsal horn neuronal hyperexcitability and the restoration of nociceptive homeostasis³⁶. In addition to NMDA blockade, ketamine interacts with muscarinic and nicotinic receptors, monoaminergic pathways (including serotonin, norepinephrine, and dopamine), voltage-gated calcium and sodium channels, and opioid receptors by blocking μ and activating κ receptors^{12,20,31}. These actions collectively enhance its analgesic effects and reduce opioid tolerance¹². Ketamine also exhibits peripheral local anesthetic properties by inhibiting action potential conduction through sodium and potassium channel blockade²⁰.

Pharmacokinetically, intravenous (IV) ketamine offers high bioavailability (~90%), a rapid onset of action (within seconds), and a short duration of effect (up to 5 minutes). In contrast, oral administration provides lower

bioavailability (~16%), a slower onset (15–20 minutes), and a longer duration of action (1–2 hours)¹⁸. Oral ketamine undergoes extensive first-pass metabolism, producing norketamine, an active metabolite with equipotent analgesic properties^{18,36}. Norketamine levels following oral administration may reach two to three times those of IV administration, making the oral-to-IV dose conversion approximately 3:1¹⁸. Reported IV dosing protocols range from 0.1 to 0.8 mg/kg/hour, with occasional total daily doses reaching up to 4800 mg, while oral dosing typically ranges from 10 to 200 mg every 6 to 8 hours¹⁸. It also described a structured IV-to-oral ketamine transition protocol using this conversion ratio, suggesting feasibility for outpatient use¹⁸. Given its multimodal mechanisms, broad pharmacological actions, and favorable pharmacodynamic profile, subanesthetic ketamine represents a rational, evidence-supported strategy for managing complex cancer pain, particularly in cases involving central sensitization and opioid resistance^{18,23,27}.

In our review of ten studies, including one randomized controlled trial (RCT), one retrospective cohort study, and eight case reports—

subanesthetic ketamine consistently demonstrated analgesic efficacy in opioid-refractory cancer pain^{8,12,18,25,30–33}. Across the case reports, patients experienced significant reductions in pain scores, with Numeric Rating Scale (NRS) improvements ranging from 33% (10 to 7) to 94% (8.5 to 0.5) (8,33). Notably, rapid pain relief was often achieved within 24 to 48 hours of ketamine initiation, even after prolonged opioid escalation had failed¹. This rapid onset of analgesia contrasts with the delayed or plateaued effects typically seen with increasing opioid doses, suggesting ketamine's broad applicability across different cancer types, metastatic sites, and baseline opioid requirements^{8,34}. In Forth et al. (2022), a pre-infusion ketamine bolus was used to identify responders, with subsequent infusion leading to substantial pain relief. The bolus also served as a bridge while waiting for continuous infusion to become available⁸.

The opioid-sparing effect observed in many reports is particularly clinically significant^{12,18,30,31}. Substantial reductions in oral morphine equivalent (OME) doses were documented, even in patients with extremely high baseline

opioid requirements. For instance, in the case reported by Grande et al. (2008), OME was reduced from 161,280 mg/day to approximately 1,485 mg/day (a 99.1% reduction) within 11 days of ketamine therapy³⁰. The retrospective cohort by Cheung et al. further supports this, with 68.6% of patients able to taper their opioid dose during ketamine infusion and a median OME decrease from 425 mg/day to 345 mg/day (10). Several studies added valuable clinical granularity, demonstrating that ketamine was effective in complex pain syndromes such as opioid-induced neurotoxicity or pelvic pain unresponsive to conventional strategies (21,23,37). These examples underscore ketamine's potential to reverse opioid-induced hyperalgesia and achieve rapid pain relief, often within 24 to 48 hours, while mitigating opioid-related adverse effects such as sedation, constipation, and tolerance(1). However, this benefit should be interpreted with caution, as much of the supporting data comes from small or uncontrolled studies.

Case reports also shed light on safety and practical implementation issues often underrepresented in clinical trials. Hallucinations and vivid dreams, while among the most common side

effects, were typically mild and manageable with agents such as lorazepam⁸. Importantly, ketamine was successfully integrated into complex multidrug regimens involving corticosteroids, sedatives, and other adjuvants^{8,25}. In Grande et al.'s report, ketamine was safely administered despite extremely high opioid loads, and Cheung et al. reported that only 4.3% of patients discontinued due to side effects, the most common being drowsiness (45.7%), hypertension (34.3%), and nightmares (25.7%) (10,30). Hardy et al. (2012) reported two serious events (bradyarrhythmia and cardiac arrest) in the ketamine group, although causality was unclear²⁹. Together, these cases demonstrate ketamine's real-world adaptability, tolerability, and therapeutic impact when individualized titration and monitoring are applied^{8,12,25,30}. In Cheung et al.'s cohort study, only 4.3% discontinued due to adverse effects, while the Importantly, no urinary complications, such as cystitis, which is more common in chronic recreational ketamine use, were reported in any of the included studies.

The pediatric application of ketamine, while less explored, also shows promise. A case by Ugur et al.

demonstrated that low-dose oral ketamine (3 mg/kg/day) effectively reduced pain scores from 8 to 0–1 in a child with cancer pain over 14 days, highlighting its feasibility when IV access is limited³³. Though optimal dosing in pediatric cancer pain remains unclear, procedural sedation studies offer indirect evidence of safety at doses up to 10 mg/kg, even in children as young as three³³. Oral ketamine produces its analgesic effect primarily through its metabolite norketamine, which peaks approximately one hour after dosing and sustains activity for several hours^{18,33}. These findings suggest a favorable safety margin and support further exploration of oral ketamine for sustained low-dose use³³. Oral administration also offers practical advantages in children: it is non-invasive, inexpensive, and device-free, although palatability remains a concern that may require flavor-masking strategies or formulation enhancements^{18,33,38}.

Contrasting these positive findings, the only included RCT (Hardy et al., 2012) did not demonstrate a statistically significant analgesic benefit over placebo²⁹. This apparent contradiction is likely due to

methodological limitations, including fixed-dose regimens (100 to 500 mg/24h SC), short treatment duration (5 days), and lack of individualized dose titration. The pain response was 31% in the ketamine group versus 27% in the placebo ($p = 0.55$), and no significant difference in opioid consumption was reported. These factors may have hindered the ability to capture ketamine's full therapeutic potential. The discrepancy highlights a critical issue in ketamine research: the absence of standardized dosing protocols and the importance of flexible, patient-tailored treatment approaches²⁹. The case reports and cohort study, where dosing was adjusted according to clinical response, may better reflect real-world clinical practice and thus demonstrate more favorable outcomes^{8,12,18,25,29–33}.

Despite the promising analgesic efficacy and opioid-sparing potential of subanesthetic ketamine in opioid-refractory cancer pain, this review highlights key limitations in the current evidence. Most studies were small, heterogeneous, and lacked control groups, which limits the generalizability of the findings^{8,10,12,18,25,29–33}. Significant variation in ketamine dosing, administration routes, treatment

durations, and outcome measures complicates efforts to draw firm conclusions or establish standardized clinical guidelines. While case reports and observational studies consistently show meaningful pain relief and opioid reductions with manageable side effects, the only randomized controlled trial included did not demonstrate statistically significant benefits, likely due to methodological constraints such as fixed dosing and short treatment periods²⁹. These factors underscore the need for larger, well-designed trials to optimize dosing, evaluate long-term safety and efficacy, and identify patients most likely to benefit. Such research is essential to clarify ketamine's role in cancer pain management and support its safe, effective use in palliative care.

CONCLUSION

Subanesthetic ketamine shows promise as an effective adjunctive treatment for opioid-refractory cancer pain, providing meaningful analgesia and significant opioid-sparing effects across various cancer types and patient populations. Evidence from case reports, a retrospective cohort study, and one randomized controlled trial indicates that ketamine, primarily administered via intravenous or subcutaneous routes at

doses ranging from 0.02 to 0.4 mg/kg/hour, can rapidly reduce pain scores, often within 24 to 48 hours, and enable substantial reductions in opioid requirements, thereby potentially improving quality of life by minimizing opioid-related side effects. While ketamine is generally well tolerated, mild neuropsychiatric adverse effects such as vivid dreams, hallucinations, and sedation have been reported but are typically manageable with supportive care. The randomized trial did not achieve statistical significance for its primary endpoint, most likely due to fixed dosing, brief treatment duration, and lack of titration, highlighting the need for individualized, flexible dosing regimens. Despite heterogeneity among studies and limited high-quality evidence, these findings support the clinical utility of subanesthetic ketamine in managing complex cancer pain, though further large-scale, rigorously designed trials are warranted to establish standardized protocols, optimize safety, and confirm long-term benefits^{8,10,12,18,25,29-33}.

CONFLICT OF INTEREST

The authors confirm that there are no financial or personal relationships that could have influenced the work

reported in this paper. All data sources described in this study are directed at the corresponding author. Ethics Approval and Consent to Participate. This article does not involve any human participants; therefore, ethical approval and informed consent were not required.

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Table 1. Summaries of Included Studies (RCT and Cohort)

No	Title	Author , year	Study Design	Center	Population	Ketamine Route	Ketamine Doses	Opioid Regimen	Intervention	Baseline OME (mg/day)	Outcome Opioid Reduce	Outcome Pain	Outcome Side Effect	Duration of Treatment
1	Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain	Hardy et al., 2012	Multisite, dose-escalation, double-blind, randomized, placebo-controlled phase III trial	Australia	185 patients randomized (93 ketamine, 92 placebo); inpatients ≥18 years with opioid-refractory chronic cancer pain (BPI ≥3); median AKPS 60; median survival 2 months	Subcutaneous	100 → 300 → 500 mg/24h SC; escalate if pain ↓ <2 BPI units or >4 breakthrough doses (after ≥80% dose delivered); reduce for toxicity; stop if intolerable or no response at 500 mg after 24h.	Various strong opioids, including oral morphine, hydromorphone, fentanyl, and oxycodone; stable doses maintained before study; patients classified as having refractory pain due to ongoing significant pain (BPI ≥3) despite high-dose opioid therapy	Escalating SC ketamine over 5 days (100 → 300 → 500 mg/day) in a fixed background opioid. Rescue analgesia allowed; opioids not increased during study.	Median 300 mg (ketamine), 410 mg (placebo); IQR 160–480 (ketamine), 258–700 mg (placebo)	N/A	No significant difference in response (31% ketamine vs 27% placebo, p = 0.55)	The ketamine group had almost double AEs (IRR 1.95), especially somnolence, dissociation, and hallucination. 2 serious AEs were possibly ketamine-related (bradyarrhythmia, cardiac arrest)	Up to 5 days
2	The Use of Ketamine in the Management of Refractory Cancer Pain in a Palliative Care Unit	Cheung et al., 2020	Retrospective cohort	Hongkong	70 cancer patients with refractory pain (2004–2018); all had cancer-related pain unrelieved by opioids (OME ≥300 mg/day); 91.4% used morphine, 65.7% had neuropathic pain; median age 56.6 y; ECOG 2–3	Subcutaneous (69 pts), IV (1 pt)	Starting: median 100 mg/day (range 50–200); Maximum: median 200 mg/day (range 50–400); titrated up to max 300 mg/day	Regular opioids: mostly morphine (91.4%), others: oxycodone, fentanyl; methadone used as an adjuvant in most patients	Continuous SC ketamine infusion titrated based on pain and side effects; opioid dose allowed to decrease by 20% daily if pain is well controlled; ketamine tapered over 2–3 days after response	425 mg/day (median OME)	Median OME reduced to 345 mg/day; 68.6% had opioid dose reduction; mean decrease –133.2 mg/day (P=0.002)	Mean NRS improved from 7.0 to 4.0 (P<0.001); 70% had ≥2-point NRS reduction; 62.9% had ≥30% reduction; 47.1% had ≥50% reduction	Mostly mild: drowsiness (45.7%), hypertension (34.3%), nightmares (25.7%); 4.3% discontinued early due to side effects	Median 10 days (IQR 6.2–15)

Abbreviation: **AE** – Adverse Event, **AKPS** – Australian-modified Karnofsky Performance Status, **BPI** – Brief Pain Inventory, **ECOG** – Eastern Cooperative Oncology Group (Performance Status), **IRR** – Incidence Rate Ratio, **IV** – Intravenous, **IQR** – Interquartile Range, mg – Milligram, **NA** – Not Available / Not Applicable, **NRS** – Numeric Rating Scale, **OME** – Oral Morphine Equivalent, **P** – P-value (statistical significance), **SC** – Subcutaneous.

Table 2. Summaries of Included Studies (Case Report)

No	Author Year	Title	Center	Diagnosis	Sex	Age	Opioid Regimen Before Admission	Average OME Before Admission (mg/day)	Other Adjuncts Used	Ketamine Route	Ketamine Bolus	Ketamine Maintenance	Opioid Bolus	Opioid Maintenance	OME Pre-ketamine (mg)	OME Post-ketamine (mg)	Opioid Reduce (%)	Baseline Pain Score	Post Intervention Pain Score	Side Effects	Duration Treatment (days)
1	Forth et al., 2022	<u>A Case Report of Subanesthetic Ketamine Bolus and Infusion for Opioid Refractory Cancer Pain</u>	USA	Gastric adenocarcinoma st IV	Male	32	Fentanyl PCA: 650 mcg/h + 200 mcg demand dose q10min	5266	Lorazepam, Haloperidol, Dexamethasone	IV	0.3 mg/kg IV bolus	0.1–0.2 mg/kg/hour IV Infusion	Hydromorphone Hydrochloride 10 mg (PCA q10min)	Hydromorphone Hydrochloride 13 mg/hour PCA	5266	2600	50.6%	10	7	Restlessness, mild nondisturbing hallucinations, and vivid dreams	6
2	Amin et al., 2014	<u>Case report: efficacy and tolerability of ketamine in opioid-refractory cancer pain</u>	USA	Metastatic breast cancer	Female	36	PO Oxycodone SR 160 mg/day + IR PRN 30 mg q6h; PO Hydromorphone 2 mg q4h PRN	480	Gabapentin, Duloxetine, Lidocaine 5% patch	IV → Oral	None	0.2–0.4 mg/kg/h IV, then PO 75 mg q8h	Hydromorphone 1.5 mg IV q15min PCA; 31 → 12 uses/day	Hydromorphone PCA basal 1.5–2 mg/h, then d/c; Oxycodone 320 mg BID	1657	640	61.4%	8	5	None	6
3	Nath et al., 2022	<u>Effectiveness of Low-Dose Ketamine Infusion in Opioid Refractory Cancer Pain: A Case Report</u>	India	Recurrent metastatic adenocarcinoma of the endometrium	Female	46	Fentanyl 75 mcg/hr IV + PRN (up to 2250 mcg/day)	225	Pregabalin 300 mg/day Paracetamol 3 g/day	IV	None	0.02–0.08 mg/kg/hr IV infusion	IV fentanyl PRN: 360–2250 mcg/day	Fentanyl IV infusion 30–75 mcg/hr, then transdermal 50 mcg/h	225	120	46.6%	7.5	1	None	4
4	Waldfoerl et al., 2016	<u>Successful Treatment of Opioid-Refractory Cancer Pain with Short-Course, Low-Dose Ketamine</u>	USA	Metastatic pancreatic neuroendocrine cancer	Male	28	Hydromorphone PCA 100 mg/h + 50 mg bolus q15min; Methadone 60 mg q8h Hydromorphone PCA (1.2 mg/h + 1.2 mg demand q6min; avg use ~7 mg/h); Methadone 120 mg/day	~50160 (Not directly reported)	Dexamethasone 6 mg IV q6h	IV	25 mg IV bolus	0.1–0.4 mg/kg/h IV infusion	Hydromorphone IV PCA: 40→8→3 mg bolus	Hydromorphone IV 100→0 mg/h + Methadone PO 60 mg q8h → 40 mg q8h	50160 (Not directly reported)	~2080 (Not directly reported)	95.9% (Not directly reported)	10	3-5	Sedation, delirium, mild hallucinations	4
5	Grande et al., 2008	<u>Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient</u>	USA	Metastatic liposarcoma	Male	43	Hydromorphone PCA (1.2 mg/h + 1.2 mg demand q6min; avg use ~7 mg/h); Methadone 120 mg/day	~4800 (Not directly reported)	Gabapentin 1800mg/day, Lorazepam, Ketorolac (90 mg/day), Memantine	IV	None	5 mg/h IV infusion	Hydromorphone IV up to 50 mg bolus	Hydromorphone IV 21-333 mg/h	161280 (Not directly reported)	~1485 (Not directly reported)	99.1% (Not directly reported)	8-9	1-3	Mild somnolence	11

6	Nishiyama, 2017	<u>Ketamine infusion was effective for severe pain of Non-Hodgkin lymphoma</u>	Japan	Non-Hodgkin lymphoma	Male	52	NA	NA	Granisetron, metoclopramide, domperidone, hydroxyzine, haloperidol	IV	10 mg IV bolus	7–10 mg/h IV infusion	None	Morphine 90 mg/day PO + 20–40 mg/day IV	210 (Not directly reported)	~60 (Not directly reported)	71.4% (Not directly reported)	8-9	1-2	None	10
7.1	Fine, 1999	<u>Low-Dose Ketamine in the Management of Opioid Nonresponsive Terminal Cancer Pain</u>	USA	Peripheral neuroectodermal tumor	Female	15	Morphine IV 160 mg/h + 60 mg bolus PRN (1 month before ketamine; in-hospital)	~11520 (Not directly reported)	Lorazepam, haloperidol	IV	5 mg (0.2 mg/kg) IV bolus	1 mg/min (60 mg/hr) IV infusion	Hydromorphone IV 4–40 mg PRN	Hydromorphone IV 20–200 mg/hr	96000 (Not directly reported)	0 (Opioids stopped)	50.0% (author reported)	NA	NA	None	2
7.2	Fine, 1999	<u>Low-Dose Ketamine in the Management of Opioid Nonresponsive Terminal Cancer Pain</u>	USA	Metastatic cervical cancer	Female	37	Morphine IV 6 mg/h	~432 (Not directly reported)	Dexamethasone, Lorazepam, Metoclopramide, Diphenhydramine, Acetaminophen	IV	5 mg (0.1 mg/kg) IV bolus	None	None	Hydromorphone IV 125–350 mg/hr	168000 (Not directly reported)	0 (Opioids stopped)	100.0 %	NA	NA	None	1
8	Ugur et al., 2009	<u>Oral ketamine for pain relief in a child with abdominal malignancy</u>	Turkey	Metastatic abdominal undifferentiated sarcoma	Male	4	PO Morphine 0.2 mg/kg q3h = 1.6 mg/kg/day (~16 mg/day)	16	None	Oral	None	3 mg/kg/day PO	None	Morphine PO 16 → 6 mg/day	16	6	62.5%	8-9	0-1	None	14

Abbreviation: **BID** – Bis in Die (twice daily), **d/c** – Discontinued, **IR** – Immediate Release, **IV** – Intravenous, **mcg** – Microgram, **mg** – Milligram, **NA** – Not Available / Not Applicable, **OME** – Oral Morphine Equivalent, **PCA** – Patient-Controlled Analgesia, **PO** – Per Os (by mouth/oral), **PRN** – Pro Re Nata (as needed), **q3h** – Every 3 Hours, **q4h** – Every 4 Hours, **q6h** – Every 6 Hours, **q8h** – Every 8 Hours, **q10min** – Every 10 Minutes, **q15min** – Every 15 Minutes, **SR** – Sustained Release.

Table 3. Risk of Bias Assessment (RCT)

Authors (RCT)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	%Yes	Risk
Kawabori et al., 2021	✓	✓	U	✓	✓	✓	✓	U	✓	✓	✓	✓	✓	85%	Low

Q1. True randomization used? **Q2.** Allocation concealed? **Q3.** Groups similar at baseline? **Q4.** Participants blinded? **Q5.** Deliverers blinded? **Q6.** Outcome assessors blinded? **Q7.** Treated identically except intervention? **Q8.** Complete follow-up described/analyzed? **Q9.** Participants analyzed in assigned groups? **Q10.** Outcomes measured the same way? **Q11.** Outcomes measured reliably? **Q12.** Appropriate statistical analysis? **Q13.** Trial design appropriate and deviations accounted for? Symbols used: ✓ – Yes; X – No; U – Unclear; N/A – Not Applicable.

Table 4. Risk of Bias Assessment (Cohort)

Authors (Cohort)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	%Yes	Risk
Cheung et al., 2020	✓	✓	✓	✓	✓	X	✓	✓	U	U	✓	64%	Moderate

Q1. Groups similar and same population? **Q2.** Exposure measured similarly? **Q3.** Exposure measured validly and reliably? **Q4.** Confounding factors identified? **Q5.** Strategies to deal with confounding? **Q6.** Participants free of outcome at start? **Q7.** Outcomes measured validly and reliably? **Q8.** Follow-up time sufficient? **Q9.** Complete follow-up or reasons explored? **Q10.** Strategies for incomplete follow-up? **Q11.** Appropriate statistical analysis? Symbols used: ✓ – Yes; X – No; U – Unclear; N/A – Not Applicable.

Table 5. Risk of Bias Assessment (Case Reports)

Authors (Case Reports)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%Yes	Risk
Forth et al., 2022	✓	✓	✓	X	✓	✓	✓	✓	87.5%	Low
Amin et al., 2014	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Nath et al., 2022	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Waldfogel et al., 2016	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Grande et al., 2008	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Nishiyama, 2017	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Fine, 1999	✓	✓	✓	X	✓	✓	✓	✓	87.5%	Low
Fatih et al., 2009	✓	✓	✓	X	✓	✓	✓	✓	87.5%	Low

Q1. Were the patient's demographic characteristics clearly described? **Q2.** Was the patient's history clearly described and presented as a timeline? **Q3.** Was the current clinical condition of the patient on presentation clearly described? **Q4.** Were diagnostic tests or methods and the results clearly described? **Q5.** Was the intervention(s) or treatment procedure(s) clearly described? **Q6.** Was the post-intervention clinical condition clearly described? **Q7.** Were adverse events (harms) or unanticipated events identified and described? **Q8.** Does the case report provide takeaway lessons? Symbols used: ✓ – Yes; X – No; U – Unclear; N/A – Not Applicable.