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Introduction

Cancer pain remains challenging in a substantial subset of patients despite optimized opioid and adjuvant therapy. Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is hypothesized to help central sensitization, opioid tolerance, and opioid-induced hyperalgesia, offering a potential pathway to analgesia in refractory cases. Given variability in patient phenotype, dosing strategies (fixed-rate vs weight-based), and outcome definitions, there remains uncertainty around optimal selection, regimen, and expected effect size.

Methods

Review Type: Narrative review
Databases Searched: PubMed, MEDLINE, and Scopus (2018-2025)
Studies Included: 10
Inclusion: Randomized controlled trials (RCTs), meta-analyses, systematic reviews, retrospective studies, and peer-reviewed guidelines
Exclusion: Animal studies, Case reports

Figures

Study	Design	Route	Primary Results	Key Limitations
Jiao et al. (2024) [Systematic Review]	Systematic review of 35 RCTs (n=2279)	IV, epidural, oral, subcutaneous, PCA	Ketamine significantly reduced pain intensity, opioid consumption, and adverse events. Most benefit was observed with IV and epidural routes.	High risk of bias in many studies; wide variability in route, dose, and timing.
Siegel et al. (2024) [Fixed vs. Weight-Based IV Dosing]	Retrospective cohort (n=105)	Continuous IV (fixed vs. weight-based)	48.6% of patients had a ≥30% reduction in pain or opioid use. No difference between fixed-rate and weight-based dosing.	Retrospective design; limited confounder control; underpowered.
Oh et al. (2021) [IV Ketamine Retrospective]	Retrospective (n=57, 192 infusions)	IV ketamine (intermittent infusions)	73.7% response rate. 71.8% had >3 weeks pain relief. SNRI co-treatment associated with better outcomes.	Retrospective data; small sample size; no control group.
Fallon et al. (2018) [Oral Ketamine RCT]	Double-blind, placebo-controlled RCT (n=214)	Oral ketamine	No difference in pain outcomes between ketamine and placebo. Analgesic benefit not statistically significant.	Mostly remission patients; ineffective route; early withdrawals.
Park et al. (2023) [Phase II CIVI Study]	Phase II single-arm trial (n=21)	Continuous IV infusion (CIVI) with titration	45% overall response rate; 35% complete responders. Safe with manageable side effects.	Small sample; early trial termination; no comparator arm.
Azari et al. (2024) [Systematic Review]	Systematic review (22 studies)	IV, IM, intrathecal, oral, subcutaneous	Intrathecal and IV ketamine consistently lowered pain and opioid use. Oral and subcutaneous routes were ineffective.	Heterogeneity in methods, dosing, and reporting across included studies.

Results

- Candidate Selection & Practical Dosing**
- Refractory cancer pain despite optimized opioids and adjuvants, neuropathic or mixed phenotypes may respond.
 - Set expectations and monitoring plans, involve palliative care/anesthesia pain teams where available.

- IV continuous infusion (common practice patterns reported)**
- Fixed-rate start: 5–10 mg/h, titrate by 5 mg/h q4–8h to effect/tolerability (often 10–40 mg/h in practice).
 - Weight-based CIVI: 0.1 mg/kg/h up-titrating toward 0.3–0.5 mg/kg/h (Phase II upper limit 0.5 mg/kg/h).
 - Dosing strategy takeaway: No clear advantage of weight-based over fixed-rate in the 2024 cohort [4].

- Other routes**
- PCEA / intrathecal: benefit signals in systematic reviews, especially peri-operative and select refractory contexts [1,2].
 - Oral: RCT negative for neuropathic cancer pain vs placebo, consider only when IV is infeasible and goals are modest [3].

- Potential co-therapies**
- Consider SNRI co-administration for neuropathic components (signal of synergy in cohort; p<0.01) [5].

- Safety (what to expect and monitor)**
- Neuropsychiatric: confusion, hallucinations, dysphoria, somnolence (dose-related; typically, reversible with rate reduction or meds).
 - Autonomic/GI: hypertension, tachycardia; nausea/vomiting.
 - Cohort data:
 - MSK (Pain Med 2021): AEs 16.7% of infusions; resolved with protocol measures [5].
 - Phase II CIVI: confusion 45%, 25% discontinued due to AEs [6].
 - Systematic review signal: no overall increase in AEs vs controls and lower opioid-type AEs in ketamine arms, likely reflecting opioid sparing [1].

- Limitations**
- Heterogeneity in populations, phenotypes (neuropathic vs nociceptive/mixed), dosing, routes, and endpoints.
 - Abstract-only studies for some modern CIVI protocols; limited long-term outcomes.
 - RCT evidence strongest against oral ketamine in neuropathic cancer pain; IV/neuraxial evidence remains promising but not definitive.

Conclusion

- Intravenous and epidural ketamine are potent adjuncts for cancer pain, especially in opioid-refractory or neuropathic pain.
- Retrospective review shows reduced pain and opioid use with titrated IV infusions and when added to SNRIs.
- Oral ketamine was not helpful. Due to heterogeneity and study biases, conclusions must be viewed with caution.
- Ketamine is a candidate third-line agent in case of failure of first-line drugs.
- More high-quality randomized trials are needed to determine dosing and patient selection.

References

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