Review Article

Efficacy of Oral and Sublingual Ketamine Formulations for Analgesia: A Systematic Review and Meta-Analysis

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Abstract

This study aimed to perform a systematic review and meta-analysis evaluating the efficacy of oral and sublingual ketamine for pain relief. A comprehensive literature search was performed across four databases: MEDLINE, CINAHL, Embase, and Web of Science. Randomized controlled trials were selected that examined oral or sublingual ketamine for pain control in either inpatient or outpatient environments, relative to any other oral or sublingual treatment, including placebo. 21 studies were incorporated into the systematic review, all involving oral ketamine, with one study directly contrasting oral and sublingual forms. Among these, 12 trials addressed oral ketamine for procedural pain, where 10 demonstrated that oral ketamine outperformed the comparator in alleviating procedural discomfort. 2 trials assessed oral ketamine for postoperative pain, both indicating a decreased need for rescue analgesics versus placebo. 5 trials explored oral ketamine for chronic pain, yielding varied outcomes. The other 2 studies consisted of one evaluating different oral ketamine dosages and the other comparing oral versus sublingual administration. 15 studies qualified for the meta-analysis. Of these, 7 studies compared oral ketamine with placebo and revealed that oral ketamine significantly outperformed placebo in pain reduction ($P < 0.01$). The remaining eight compared oral ketamine with other oral agents, including methadone, codeine, midazolam, and dexmedetomidine, and found no notable advantage for oral ketamine in pain mitigation ($P = 0.18$). Findings indicate that oral ketamine serves as an efficacious analgesic option, particularly in procedural contexts.

Keywords: Pain, Analgesia, Ketamine, Sublingual, Oral

Introduction

Pain, a universal human experience, often eludes effective management [1]. It drives up to 70% of global emergency department visits [2]. Inadequate pain control also significantly contributes to the worldwide disease burden. For example, the 2019 Global Burden of Disease study reported that painful musculoskeletal disorders—such as rheumatoid arthritis, osteoarthritis, low back pain, neck pain, and gout—accounted for 5.9% of total age-standardized disability-adjusted life years (DALYs) [3]. Despite this burden, safe and effective long-term pharmacological options for pain relief remain limited. Opioids, a mainstay for acute pain, carry risks including respiratory depression, tolerance, and dependence with prolonged use [4]. Globally, opioids are the leading cause of drug-related harm, with rising misuse of prescription opioids [5]. Consequently, there is a pressing need for suitable opioid alternatives.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, offers an alternative for acute pain management [6]. Intravenous ketamine is well-established as an effective and well-tolerated option for acute pain, supported by level 1 evidence [1]. Research also suggests it may mitigate opioid-induced hyperalgesia and prevent the progression from acute to chronic pain [6-8].

Given the efficacy of intravenous ketamine in acute pain, alternative administration routes, such as oral and sublingual, have been explored. Unlike intravenous delivery, oral and sublingual formulations allow for easy self-administration, making them suitable for outpatient settings. Oral ketamine, administered as a swallowed lozenge or liquid, is absorbed through the stomach and intestines, with a bioavailability of 20%–25% due to significant first-pass metabolism [9, 10]. Its active metabolite, norketamine, may contribute to its analgesic effects [11]. Sublingual ketamine, delivered as a

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lozenge or wafer and absorbed via the oral mucosa, has a bioavailability of 24%–30% [9, 10]. Oral administration is considered less effective than intravenous due to lower bioavailability [12], and its variable absorption may increase psychomimetic side effects [12].

Oral and sublingual ketamine formulations are available for off-label use in several countries [1], including the United Kingdom [13]. However, they lack approval from regulatory bodies such as the United Kingdom's National Institute for Health and Care Excellence (NICE), the United States Food and Drug Administration (FDA), and the Australian Therapeutic Goods Administration (TGA) [13-15]. This is partly due to the need for further evaluation of their safety and efficacy. As a widely used psychoactive substance globally, ketamine carries a significant risk of abuse [12]. Thus, a thorough assessment of its therapeutic profile is essential before clinical endorsement.

The evidence for oral and sublingual ketamine in pain management is diverse, with incomplete synthesized secondary data. A systematic review on oral ketamine for sedation in pediatric dental procedures found it effective in reducing anxiety and improving behavioral compliance [16]. While this suggests safety and some efficacy in pediatric populations, it did not focus on analgesia. A Dutch systematic review on oral ketamine for chronic pain found no consistent dose-response relationship, proposing it as a potential adjunct for complex chronic pain [11]. Another systematic review, focusing on oral ketamine's antidepressant effects rather than analgesia, reported significant benefits with good tolerability [17-21]. A narrative review cautioned against oral ketamine due to its unpredictable bioavailability and abuse potential [12]. None of these reviews included meta-analyses or specifically evaluated oral and sublingual ketamine for acute pain. Therefore, this study aims to conduct a systematic review and meta-analysis to assess (1) the analgesic efficacy of oral ketamine compared to another agent or placebo, (2) the analgesic efficacy of sublingual ketamine compared to another agent or placebo, and (3) the comparative analgesic efficacy of oral versus sublingual ketamine.

Materials and Methods

This systematic review and meta-analysis adhered to the standards outlined in the Cochrane Handbook and the PRISMA guidelines for systematic reviews and meta-analyses.

Search Strategy and Data Sources

We conducted comprehensive searches across MEDLINE, CINAHL, Embase, and Web of Science databases, applying no filters or restrictions. To expand the scope, we hand-searched the reference lists of pertinent publications. Details on the keywords and search strings are provided in Appendix 1.

Inclusion and Exclusion Criteria

Studies Included

Eligible research encompassed randomized controlled trials (RCTs) that examined oral or sublingual ketamine as a treatment for pain—whether in hospital or community settings—against any other oral or sublingual option, including placebo. We included participants from all age ranges and imposed no cutoff for publication dates. Only full-text publications were considered.

Studies Excluded

We ruled out investigations involving other ketamine delivery methods, like intravenous, subcutaneous, topical, epidural, or intramuscular routes. Non-human experiments and those performed in non-patient contexts (for instance, experimentally induced pain in healthy individuals) were not selected. Likewise, we disregarded conference abstracts, study protocols, opinion pieces, and correspondence letters.

Process for Selecting Studies

All search results were loaded into Covidence software (developed by Veritas Health Innovation in Melbourne, Victoria, Australia), and duplicate entries were purged. Two investigators separately reviewed titles and abstracts from the entire set of records; a third party settled disputes. Full-text evaluations of shortlisted papers were then carried out independently by three investigators, with consensus achieved via group deliberation.

Results and Discussion

Pain score reduction served as the primary endpoint. Various tools were employed for pain evaluation in the narrative overview, including the Children's Hospital of Eastern Ontario Pain Scale, visual analog scales, numeric rating scales, verbal rating scales, the Neonatal Infant Pain Scale, and the FLACC (face, legs, activity, cry, consolability) scale. Additional endpoints covered the onset time for initial pain relief, time to substantial pain reduction, length of pain-relieving effects, the share of responders to analgesia, and the interval before requiring supplementary pain medication. In the meta-analysis, we relied on the standardized mean difference (SMD) for pain scores, including associated variance estimates.

Evaluation of Bias

One investigator applied the Cochrane Risk of Bias 2 (RoB 2) tool to scrutinize potential biases in every qualifying study.

Synthesis of Data

We synthesized the findings narratively from the selected studies. To meet the review's goals, we grouped results into sections: oral ketamine for managing acute pain during procedures in adults and children; oral ketamine for acute pain following surgery in adults; oral ketamine for ongoing chronic pain in adults; and direct comparisons of oral versus sublingual ketamine for pain control in adults (with just a single study on the sublingual form).

For the quantitative pooling, we used RevMan 5, developed by the Cochrane Collaboration (based in London, UK), to conduct a meta-analysis. This was restricted to RCTs pitting oral ketamine against a control arm (such as placebo or another active agent). We omitted studies that failed to report average pain scores across groups; the reasoning behind these decisions is summarized in **Table 1**. Owing to the diversity of pain assessment methods, we calculated SMDs and variances using Hedges' (g) adjustment in RevMan 5. Pooled estimates were then generated via the inverse-variance technique, testing both fixed-effect and random-effect approaches. The latter also accounted for heterogeneity by estimating and weighting based on between-study variation.

Table 1. Omitted studies that failed to report average pain scores across groups.

Study	Sample size	Country	Age group	Pain type	Intervention	Comparison	Key findings	Conclusions	Included in meta-analysis
Oral ketamine for acute procedural pain									
Bagheri *et al.* [22]	N = 160, single center	Iran	Pediatric (3–6 years)	Procedural (IV insertion)	Oral ketamine 3 mg/kg	Placebo	CHEOPS median: Ketamine = 6 (IQR 5–8)	Oral ketamine 3 mg/kg is effective for IV insertion	included (ketamine vs placebo)
Barkan *et al.* [23]	N = 60, single center	Israel	Pediatric (1–10 years)	Procedural (suturing)	Oral ketamine 5 mg/kg + midazolam 0.5 mg/kg	Placebo + midazolam 0.5 mg/kg	VAS mean ± SD reported	Effective for suturing pain	Included (ketamine vs placebo)
Bozorgi *et al.* [24]	N = 102, single center	Iran	Pediatric (2–10 years)	Procedural	Oral ketamine 5 mg/kg + midazolam 0.5 mg/kg	Oral promethazine 1 mg/kg + midazolam 0.5 mg/kg	VAS mean ± SD reported	Ketamine outperformed promethazine	Included (ketamine vs other drugs)
Ezike and Odiakosa [21]	N = 240, single center	Nigeria	Adult	Procedural (burns dressing)	Oral ketamine (doses: 0.5, 2, 4, 6, 8, 10 mg/kg)	No control group	VRS ≤ 2: 0% (0.5, 2 mg/kg), 25% (4 mg/kg), 65% (6 mg/kg), 92.5% (8 mg/kg), 95% (10 mg/kg), P < 0.05	Minimum effective dose 6 mg/kg; higher doses linked to complications	Not included (no non-ketamine control)
Humphries *et al.* [25]	N = 19, single center	USA	Pediatric (≤ 12 years)	Procedural (burns dressing)	Oral ketamine 10 mg/kg	Oral codeine 0.5 mg/kg + diphenhydramine 2.5 mg/kg + paracetamol 300 mg	VAS: Ketamine = 1.7 ± 0.8, Comparator = 7.1 ± 0.9, P < 0.05	Ketamine is superior to the codeine combination	Included (ketamine vs other drugs)
Kaviani *et al.* [26]	N = 36, single center	Iran	Adult and adolescent (15–45 years)	Procedural (dental)	Oral ketamine 10 mg	Placebo	VAS: Ketamine = 0.61 ± 1.09, Placebo = 1.61 ± 1.33, P = 0.019; reduced LA and analgesia use	Ketamine is superior in pain scores and reduced analgesic needs	Included (ketamine vs placebo)
Kundra *et al.* [27]	N = 60, single center	India	Adult	Procedural (burn dressing)	Oral ketamine 5 mg/kg (crossover)	Oral dexmedetomidine 4 mg/kg (crossover)	VAS reduction: Ketamine = 2.6 ± 0.6, Dexmedetomidine = 3.8 ± 0.8, p<0.05	Ketamine outperformed dexmedetomidine	Included (ketamine vs other drugs)
Majidinejad *et al.* [28]	N = 86, single center	Iran	Adult	Procedural (gastroscopy, colonoscopy)	Oral ketamine 5 mg/kg	Placebo	VAS: Ketamine = 2.4 ± 1.8, placebo = 5.81 ± 1.48, P < 0.001	Ketamine is significantly better than a placebo	Included (ketamine vs placebo)
Modekwe *et al.* [29]	N = 121, single center	Nigeria	Term neonates	Procedural (circumcision)	Oral ketamine 10 mg/kg	Placebo (sucrose)	NIPS: Ketamine = 3.93 ± 1.58, Placebo = 4.88 ± 0.45, P < 0.001	Ketamine is superior to a placebo	Included (ketamine vs placebo)

Norambuena *et al*. [30]	N = 60, single center	Chile	Pediatric (1–5 years)	Procedural (burns dressing)	Oral ketamine 5 mg/kg + midazolam 0.5 mg/kg	Oral paracetamol 10 mg/kg + codeine 1 mg/kg + midazolam 0.5 mg/kg	CHEOPS: Ketamine = 7.4 (95% CI 4–12), Comparator = 8.9 (95% CI 4–13), P = 0.0245	Ketamine is superior to paracetamol/codeine	Included (ketamine vs other drugs)
Qureshi *et al*. [31]	N = 30, single center	USA	Pediatric (1–7 years)	Procedural (suturing)	Oral ketamine 10 mg/kg	Placebo	Tolerance (4-point Likert): Ketamine better for LA injection and suturing, P = 0.001, 0.009	Ketamine improved tolerance compared to the placebo	Included (ketamine vs placebo)
Rubinstein *et al*. [32]	N = 68, single center	Israel	Pediatric (1–10 years)	Procedural (suturing)	Oral ketamine 5 mg/kg	Oral midazolam 0.7 mg/kg	VAS (parent-reported): Ketamine = 5.07 ± 0.75, Midazolam = 3.68 ± 0.7, P > 0.05	No significant difference	Included (ketamine vs other drugs)
Singh *et al*. [33]	N = 112, single center	India	Pediatric (3–10 years)	Procedural (dental)	Oral ketamine 8 mg/kg	Oral dexmedetomidine (3, 4, 5 mg/kg)	Intraop FLACC: Ketamine = 3.43 ± 1.03, Dex (3, 4, 5 mg/kg) = 5.04 ± 1.37, 4.57 ± 1.23, 3.64 ± 1.28, P < 0.001; Postop FLACC also superior	Ketamine is better than dexmedetomidine 3 and 4 mg/kg, similar to 5 mg/kg	Included (ketamine vs other drugs)
Oral ketamine for acute postoperative pain									
Heidari *et al*. [34]	N = 72, single center	Iran	Adult	Acute postoperative	Oral ketamine 1 mg/kg every 8 hours for 24 h	Placebo	VAS (at 2, 4, 8, 16, 24 h): Ketamine lower, P < 0.05; Morphine use: Ketamine = 10.1 mg, Placebo = 13.4 mg, P < 0.05; time to rescue: Ketamine = 3.5 h, Placebo = 1.9 h, P < 0.05	Ketamine is superior to a placebo	Included (ketamine vs placebo)
Sakata *et al*. [35]	N = 30, single center	Brazil	Adult	Acute postoperative	Oral S(+)-ketamine 10 mg + morphine 10 mg	Placebo + morphine 10 mg	NRS: No significant difference, P > 0.05; Fewer ketamine patients needed extra analgesia (26.7% vs 6.7%, P < 0.05)	No difference in pain scores, but less rescue analgesia was needed	Included (ketamine vs placebo)
Oral ketamine for chronic pain									
Fallon *et al*. [36]	N = 214, multicenter	UK	Adult	Cancer-related neuropathic (chronic), 30-day trial	Oral ketamine (40–400 mg/day)	Placebo	No difference in analgesia duration or response rates, P > 0.05	No significant benefit over placebo	Not included (no pain scores reported)
Haines and Gaines [37]	N = 21, single center	UK	Adult	Chronic neuropathic, 8-week trial	Oral ketamine (20–100 mg/day)	Placebo	14% responded to ketamine, but ~50% had side effects	Limited benefit for some patients	Not included (incomplete pain scores)
Ishizuka *et al*. [38]	N = 30, Single center	Brazil	Adult	Cancer pain (chronic), 4-week trial	Oral S(+)-ketamine 10 mg every 8 h + morphine	Placebo + morphine	No significant difference in relief rates, P > 0.05	No benefit over placebo	Not included (no mean/median pain scores)
Jafarinia *et al*. [39]	N = 46, single center	Iran	Adult	Chronic headache (+ depression), 6-week trial	Oral ketamine 50 mg every 8 h (150 mg/day)	Diclofenac 50 mg every 8 h (150 mg/day)	VAS change: No significant difference, P > 0.05	No difference compared to diclofenac	Included (ketamine vs other drugs)

Rigo *et al*. [40]	N = 42, Single center	Brazil	Adult	Chronic neuropathic, 90-day trial	Oral ketamine 30 mg every 8 h	Methadone 3 mg every 8 h or combination	VAS % reduction: No significant difference, P > 0.05; Ketamine better for allodynia	Ketamine is comparable to methadone and superior for allodynia	Included (ketamine vs other drugs)
Oral vs Sublingual Ketamine									
Chong *et al*. [20]	N = 23, single center	Australia	Adult	Acute breakthrough (nociceptive, neuropathic, procedural), crossover	Sublingual ketamine 50 mg + oral placebo	Oral ketamine 50 mg + sublingual placebo	NRS (1 h): No difference, P = 0.63; Time to first effect: P = 0.069; Time to meaningful analgesia: Sublingual = 10.8 min, Oral = 29.4 min, P = 0.02	Sublingual ketamine is faster for meaningful analgesia	Not included (no non-ketamine control)

The database searches across the four sources yielded 426 articles in total. An additional two studies were identified through reference list reviews of key publications. Following duplicate elimination, 249 abstracts underwent screening, resulting in 47 potentially relevant full-text articles retrieved for detailed evaluation. 5 articles were discarded because their full texts were inaccessible. Consequently, 42 full-text articles were thoroughly examined for eligibility. Of these, 21 were rejected because they involved inappropriate comparators, mismatched outcome measures, incorrect interventions, unsuitable participant groups, or non-qualifying administration routes. This process ultimately selected 21 articles for incorporation into the systematic review **(Figure 1)**.

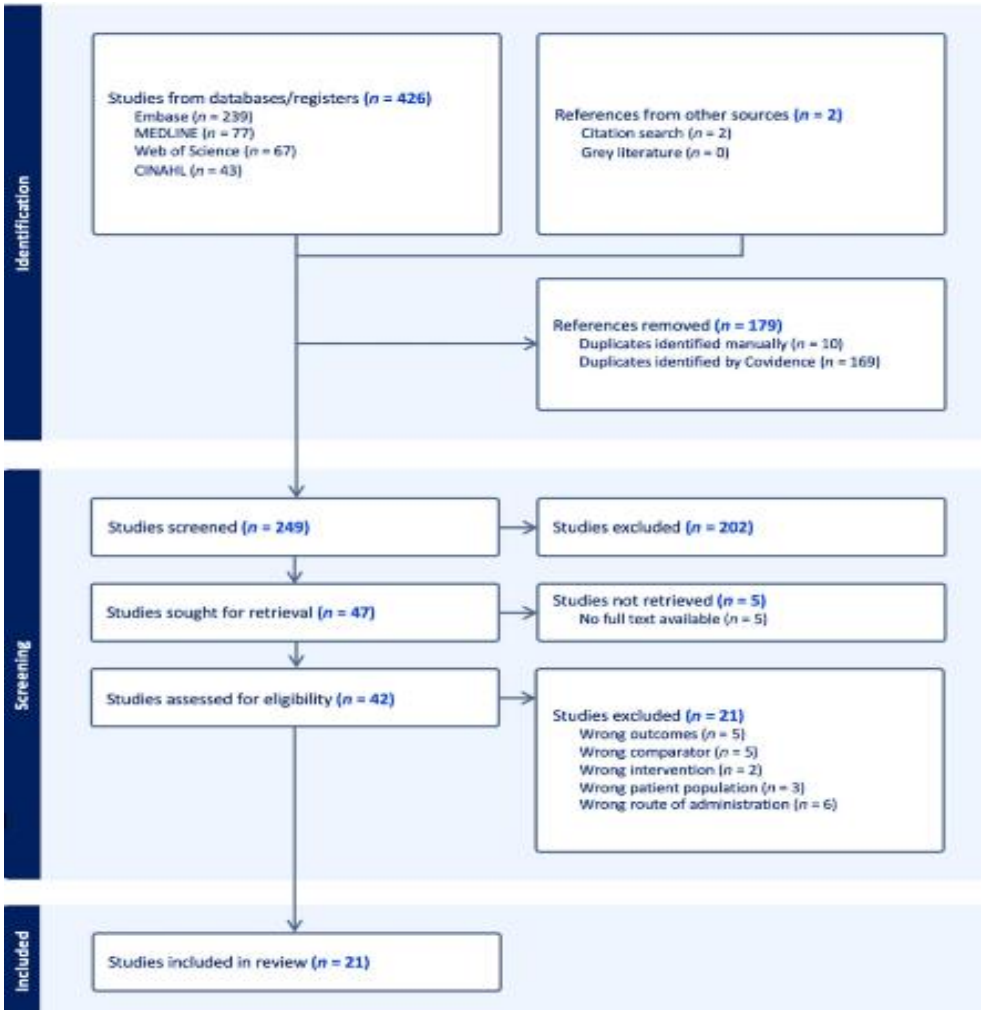

Figure 1. PRISMA flowchart outlining article selection process.

Characteristics of Included Studies

Among the 21 selected studies, nine targeted pediatric groups (aged ≤ 14 years), while 12 examined adolescent and adult cohorts (aged ≥ 15 years). Publications spanned 1995–2022 and came from locations including Iran [6], Brazil [3], Israel [2], the United States (USA) [2], Nigeria [2], India [2], the United Kingdom (UK) [2], Chile [1], and Australia [1]. Enrollment varied from 19 to 240 subjects per trial. Each study investigated oral ketamine's efficacy, with one trial [20] contrasting it against sublingual ketamine and another [21] testing a spectrum of oral ketamine dosages (0.5–10 mg/kg). All nine pediatric trials addressed acute nociceptive pain from procedures involving IV placement, suturing, burn care, or newborn circumcision. In the 12 adolescent/adult trials, seven dealt with acute nociceptive discomfort (procedural or postoperative), and five with persistent conditions like neuropathic pain, ongoing headaches, or malignancy-associated pain. **Table 1** outlines the features of these 21 trials.

Oral Ketamine for Acute Procedural Pain Management in Adults and Paediatrics

Thirteen investigations (nine pediatric, four adult) explored oral ketamine's role in handling acute procedural pain, involving 1154 individuals overall [21–33]. Across 12 trials, oral ketamine faced off against placebo [22, 23, 26, 28, 29, 31], dexmedetomidine [27, 33], promethazine [24], midazolam [32], or an opioid-paracetamol mix [25, 30]. Pediatric dosing ranged from 3 mg/kg to 10 mg/kg, while adults received 5 mg/kg or a one-time 10-mg dose. Eleven trials showed oral ketamine outperforming alternatives in easing procedural discomfort ($P < 0.05$). The exceptions were Barkan *et al*. [23], who detected no notable gap in pain ratings for pediatric subjects on 5 mg/kg oral ketamine versus placebo, and Rubinstein *et al*. [32], who saw no meaningful variance in scores for kids given 5 mg/kg oral ketamine versus 0.7 mg/kg midazolam. These two trials carried a high bias risk [23, 32].

A single trial assessed escalating oral ketamine levels from 0.5 mg/kg to 10 mg/kg among adults [21]. Researchers observed that higher amounts boosted pain-relieving power yet raised the incidence and intensity of adverse reactions. They identified 6 mg/kg as the optimal adult dosage, weighing the benefits against the drawbacks [21].

Oral Ketamine for Acute Postoperative Pain Management in Adults

Two trials [34, 35], totaling 102 adults, probed oral ketamine for postoperative discomfort control. Heidari *et al*. [34] reported that it markedly outdid the placebo by lowering pain levels, reducing supplementary analgesic needs, and delaying the need for initial rescue dosing. Sakata *et al*. [35] identified no key variances in pain intensity or rescue timing, but confirmed that oral ketamine sharply decreased demands for extra pain relief.

Oral Ketamine for Chronic Pain in Adults

Five trials [36-40], encompassing 353 participants, evaluated oral ketamine for enduring pain, using varied protocols. Doses spanned 30 to 400 mg/day, given from once daily up to every 8 hours, across 30–90-day spans. It was benchmarked against placebo [36-38], diclofenac [39], and methadone [40]. Applications covered cancer-linked pain [36, 38], non-cancer neuropathic issues [37, 40], and chronic headache sufferers [39]. Fallon *et al*. [36] and Ishizuka *et al*. [38] noted no substantial edge over placebo for pain handling. Jafarinia *et al*. [39] saw equivalence to diclofenac in score reductions. Rigo *et al*. [40] deemed it notably stronger than methadone for allodynia but equal on other metrics. Haines and Gaines [37] estimated that about 10% of chronic neuropathic pain patients could benefit from oral ketamine without significant side effects.

Oral Versus Sublingual Ketamine in Adults

In a crossover trial featuring 23 adults and a 24-hour washout interval, Chong and Schug [20] examined 50 mg sublingual ketamine against 50 mg oral ketamine for treating breakthrough acute pain. The investigation revealed that sublingual delivery provided faster clinically relevant pain alleviation (average 10.8 minutes) than the oral route (average 29.4 minutes). In contrast, pain intensity ratings and other metrics remained broadly equivalent across both methods [20].

Meta-Analysis

Oral Ketamine Versus Placebo

The meta-analysis incorporated seven investigations that pitted oral ketamine against placebo [23, 26, 28, 29, 31, 34, 35]. Results indicated a notable decrease in discomfort levels, favoring oral ketamine. Under the fixed-effects approach, the standardized mean difference was -1.01 (95% confidence interval [CI], -1.21 to -0.80), yielding a Z-value of 9.55 ($P < 0.001$) **(Figure 2)**. The random-effects approach likewise supported ketamine's advantage (SMD -1.05, 95% CI -1.65 to -0.45), with a Z-value of 3.41 ($P < 0.001$) **(Figure 3)**. With an I^2 value of 87%, considerable variability was evident among the included research.

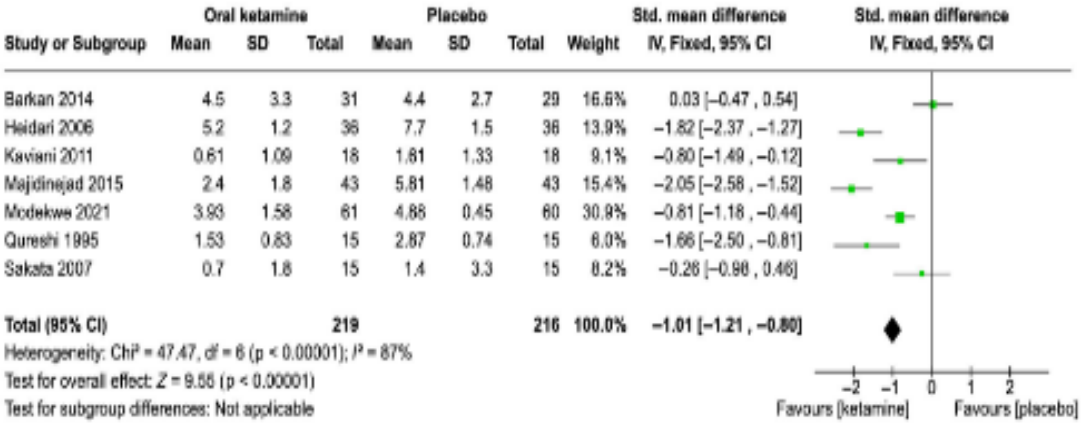

Figure 2. Meta-analysis comparing oral ketamine to placebo (fixed-effects model); CI = confidence interval; df = degrees of freedom; IV =intravenous; Std. = standard; and SD = standard deviation.

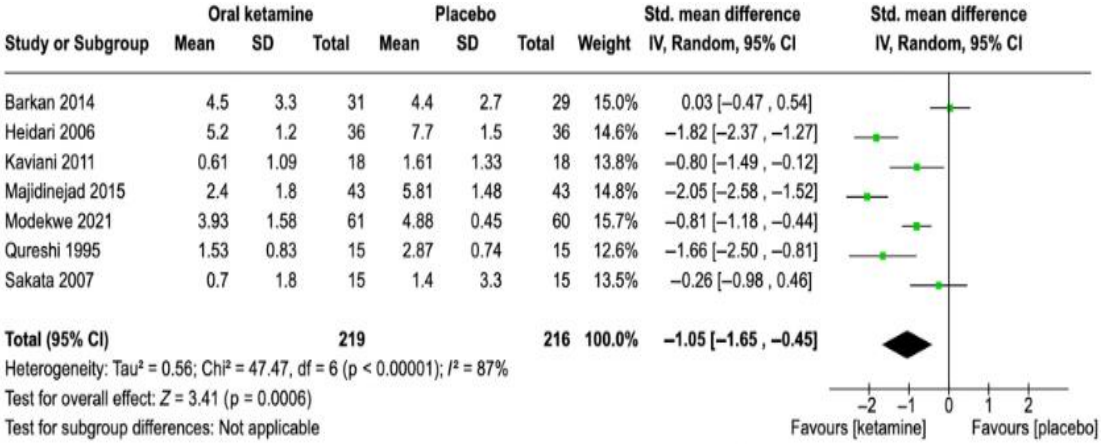

Figure 3. Meta-analysis comparing oral ketamine to placebo (random-effects model); CI = confidence interval; df = degrees of freedom; IV = intravenous; Std. = standard; and SD = standard deviation.

Oral Ketamine Versus Other Drugs

The meta-analysis encompassed eight trials that evaluated oral ketamine against various alternative medications [24, 25, 27, 30, 32, 33, 39, 40]. Overall, no meaningful variation in pain-relieving performance emerged between oral ketamine and these other oral agents **(Figures 4 and 5)**. For the fixed-effects analysis, the standardized mean difference (SMD) was -0.15 (95% confidence interval [CI], -0.36 to 0.06), accompanied by a Z-score of 1.35 (P = 0.18) **(Figure 4)**. Meanwhile, the random-effects analysis produced an SMD of -0.51 (95% CI -1.54 to 0.53), with a Z-score of 0.96 (P = 0.34) **(Figure 5)**. An I^2 value of 95% pointed to extreme inconsistency across the studies. In essence, these outcomes imply that oral ketamine offers no advantage over the examined alternatives—such as promethazine, codeine, diphenhydramine, paracetamol, diclofenac, dexmedetomidine, midazolam, and methadone—in terms of pain mitigation.

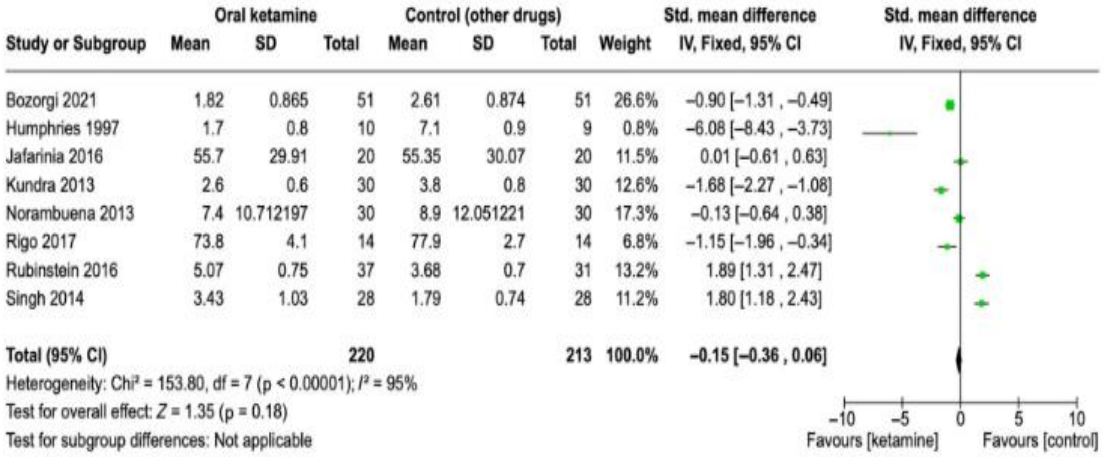

Figure 4. Meta-analysis comparing oral ketamine to other drugs (fixed-effects model); chi 2 = chi-square; CI = confidence interval; df =degrees of freedom; I2 = inconsistency; IV = intravenous; Std. = standard; SD = standard deviation; and Z = Z-score.

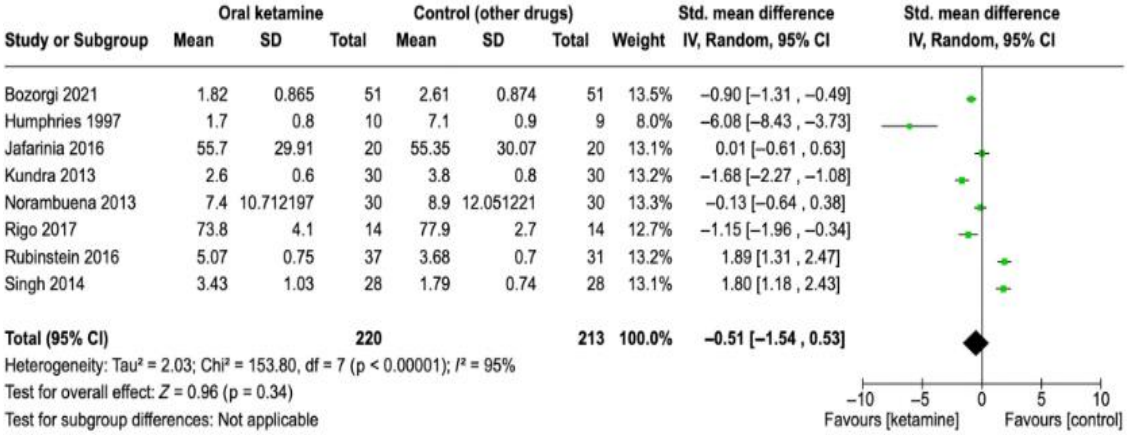

Figure 5. Meta-analysis comparing oral ketamine to other drugs (random-effects model); chi 2 = chi-square; CI = confidence interval; df =degrees of freedom; I2 = inconsistency; IV = intravenous; Std. = standard; SD = standard deviation; and Z = Z-score.

Risk of Bias Assessment

Of the 21 included studies, 15 were assessed as having some concerns or being at high risk of bias **(Table 2)**.

Table 2. Assessment of risk of bias of included studies using Version 2 of the Cochrane risk-of-bias (RoB-2) tool

Study	Domain 1: Randomization process	Domain 2: Deviations from intended interventions	Domain 3: Missing outcome data	Domain 4: Measurement of outcome	Domain 5: Selection of reported results	Overall risk of bias assessment	Anticipated bias direction
Bagheri *et al.* [22]	Low	Low	Low	Low	Some concerns	Some concerns	Unpredictable
Barkan *et al.* [23]	Low	Low	High	Some concerns	Low	High	Favours comparator
Bozorgi *et al.* [24]	Low	Low	Low	Low	Some concerns	Some concerns	Unpredictable
Chong *et al.* [20]	Low	Low	Some concerns	Low	Some concerns	High	Unpredictable

Ezike and Odiakosa [21]	Some concerns	Some concerns	High	Some concerns	Low	High	Favours lower doses of ketamine
Fallon *et al.* [36]	Low	Low	Low	Low	Low	Low	Not applicable (N/A)
Haines *et al.* [37]	Low	Low	High	Low	Low	High	Favours ketamine
Heidari *et al.* [34]	Low	Low	Low	Low	Low	Low	N/A
Humphries *et al.* [25]	Low	Low	Low	Some concerns	Low	Some concerns	Unpredictable
Ishizuka *et al.* [38]	Low	Some concerns	Some concerns	Low	Low	Some concerns	Unpredictable
Jafarinia *et al.* [39]	Low	Low	Low	Low	Some concerns	Some concerns	Unpredictable
Kaviani *et al.* [26]	Some concerns	Low	Low	Low	Low	Some concerns	N/A
Kundra *et al.* [27]	Low	Low	Low	Low	Low	Low	N/A
Majidinejad *et al.* [28]	Low	Low	Low	Low	Some concerns	Some concerns	N/A
Modekwe *et al.* [29]	Low	Low	Low	Some concerns	Low	Some concerns	N/A
Norambuena *et al.* [30]	Some concerns	Low	Low	Low	Low	Some concerns	N/A
Qureshi *et al.* [31]	Low	Low	Low	Low	Low	Low	N/A
Rigo *et al.* [40]	Low	Low	Some concerns	Low	Some concerns	High	Favours ketamine
Rubinstein *et al.* [32]	Low	Low	High	Low	Low	High	Favours ketamine
Sakata *et al.* [35]	Low	Low	Low	Low	Low	Low	N/A
Singh *et al.* [33]	Low	Low	Low	Low	Low	Low	N/A

This study is among the first to evaluate the efficacy of oral and sublingual ketamine in managing both acute and chronic pain. Following an extensive literature search with predefined criteria and a meta-analysis, the findings indicate that oral ketamine is an effective analgesic for acute nociceptive pain, especially in procedural contexts [9,10]. Given that oral ketamine has a bioavailability of at least 20%, it is reasonable to infer that, when dosed appropriately, it could be as effective as intravenous ketamine for acute pain management [9, 10]. Further studies are needed to confirm oral ketamine's effectiveness in acute nociceptive pain and to define its safety profile, including establishing a safe and effective dosage range. For sublingual ketamine, a single small study suggested it may offer analgesic effects comparable to oral ketamine for acute breakthrough pain, with a faster onset of meaningful pain relief [20]. However, more high-quality research is required to substantiate these findings.

The meta-analysis revealed that oral ketamine significantly reduced pain scores compared to placebo. Still, it was not significantly more effective than other drugs, such as promethazine, codeine, diphenhydramine, paracetamol, diclofenac, dexmedetomidine, midazolam, or methadone. These results suggest that while oral ketamine may contribute to pain reduction, it may not be superior to existing treatment options.

These findings are consistent with prior systematic reviews exploring ketamine's sedative and anxiolytic effects in procedural pain. For instance, a systematic review of ketamine in pediatric dentistry found that oral ketamine effectively reduced procedural anxiety and improved behavioral compliance [16]. Similarly, a meta-analysis of 20 studies comparing oral midazolam to a midazolam/ketamine combination for pediatric procedural sedation reported comparable anxiolytic effects, with the ketamine/midazolam group showing greater cooperation during intravenous

insertion, indicating additional analgesic benefits of ketamine [41]. Although these reviews did not specifically focus on oral ketamine's analgesic effects, their findings support its utility in painful procedures.

In chronic pain management, five studies in this analysis found oral ketamine to be no more effective than comparators. These results align with a systematic review by Blonk *et al*. which found no consistent dose-response relationship and suggested that oral ketamine has a limited role in complex chronic pain when other treatments fail [11]. Similarly, a narrative review by Nowacka and Borczyk concluded that ketamine's use in chronic pain remains controversial and requires further investigation [42]. In contrast, a systematic review by Bredlau *et al*. found that oral ketamine, among other routes, could be a valuable adjunct for managing refractory cancer pain [43]. These discrepancies may arise from differences in study methodologies [42, 43].

Conclusion

The differences in findings may stem from factors such as including observational studies and targeting a more specific group of patients with refractory cancer pain. Notably, there is currently a lack of robust secondary evidence for the efficacy of intravenous ketamine in chronic pain management, mainly due to inconsistent results from primary studies [1, 42]. This highlights the importance of cautious use of ketamine for chronic pain until more rigorous, well-designed studies are conducted.

This systematic review identified only one randomized controlled trial examining sublingual ketamine for pain management, indicating a need for further primary research in this area. Given the comparable bioavailability of oral (20%–25%) and sublingual (24%–30%) ketamine, findings on oral ketamine might apply to sublingual ketamine [9, 10]. However, high-quality primary research is essential to verify the safety, efficacy, and onset of sublingual ketamine before it can be implemented in clinical practice.

In this systematic review and meta-analysis, we conducted an extensive literature search across four databases, using predefined criteria to select relevant studies. This approach ensured a broad inclusion of studies evaluating the effectiveness of oral and sublingual ketamine for acute and chronic pain management. Only randomized controlled trials were included, and a meta-analysis was performed to assess the magnitude, strength, and direction of effects, enhancing the reliability and validity of the results. Strict risk-of-bias criteria revealed that over half of the studies had some risk of bias, which lowers confidence in the conclusions. Study heterogeneity further reduced the precision of findings. Only one study focused on sublingual ketamine, leaving the second and third objectives related to sublingual ketamine underexplored. Similarly, the limited number of studies on oral ketamine for acute postoperative pain and the methodological variability in chronic pain studies restricted the interpretation of results.

This study supports the use of oral ketamine as a feasible option for managing procedural pain. Additional primary research is needed to confirm its safety and determine optimal dosing, frequency, and duration for procedural pain and other acute pain scenarios, such as postoperative care. Likewise, further studies are required to evaluate the safety and efficacy of oral and sublingual ketamine for long-term chronic pain management [1, 9, 10, 42].

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