Benefits and harms of Ketamine for management of chronic non-cancer pain

Comparative effectiveness of Ketamine for management of chronic non-cancer pain: A systematic review and network meta-analysis of randomized controlled trials

By Sara Moradi, DDS

Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2024)
Hamilton, Ontario (Health Research Methods, Evidence, and Impact)

TITLE: Comparative effectiveness of Ketamine for management of chronic non-cancer pain: A systematic review and network meta-analysis of randomized controlled trials

AUTHOR: Sara Moradi

SUPERVISOR: Dr. Behnam Sadeghirad

NUMBER OF PAGES: 160 + xiii

Abstract:

Background: Chronic non-cancer pain (CNCP) is a prevalent condition, imposing significant burden on healthcare systems. Ketamine is suggested as a potential intervention for CNCP management. We conducted a systematic review and network meta-analysis to assess ketamine's effects in adults with CNCP.

Methods: We searched Medline, Embase, CINAHL, and Cochrane CENTRAL up to January-2024 for randomized trials involving adults with CNCP, comparing ketamine with placebo, usual care, or other interventions. Reviewers independently assessed trial eligibility, extracted data, and evaluated risk-of-bias using the Cochrane tool. A random-effects network meta-analysis was performed. We assessed evidence certainty using GRADE.

Results: We included 38 trials, with the following comparisons made between ketamine and placebo, using 0-10 VAS: At <30 minutes, ketamine may slightly reduce pain intensity (-1.32, 95% CI: [-1.73 to -0.90], low-certainty). At 1-3 hours follow-up, ketamine may slightly reduce pain intensity (MD: -1.25, (95% CI: [-1.76 to -0.74], low-certainty). At 3-to-7 days follow-up, ketamine may have little to no effect on pain intensity (MD: -1.34, 95% CI: [-2.29 to -0.39], low-certainty). At 3-to-5 weeks follow-up, ketamine likely results in no pain reduction (MD: -0.99, 95% CI: [-2.00 to 0.03], moderate-certainty). At beyond 5 weeks the evidence about ketamine pain reduction is very uncertain (MD: -1.09, 95% CI: [-1.86 to -0.32], very-low-certainty). Ketamine had no effect on physical functioning. Compared to placebo, ketamine may result in a slight increase in the risk of gastrointestinal adverse events (RR: 3.97, 95% CI: [2.18 to 7.22], RD: 12%, 95% CI: [5% to 25%], very-low-certainty), an increase in risk of dizziness (RR: 3.66, 95% CI: [1.25 to 10.74], RD: 11%, 95% CI: [1% to 40%], low-certainty), may increase the risk of fatigue, somnolence, and sedation (RR: 2.89, 95% CI: [1.84 to 4.53], RD: 27%, 95% CI: [12% to 50%], low-certainty), may increase of the incidence of dissociative symptoms (RR: 4.22, 95% CI: [2.20 to 8.10], RD: 17%, 95% CI: [6% to 37%], low-

certainty), and it may result in a slight increase in the risk of visual impairment (RR: 10.21, 95% CI: [2.86 to 36.42], RD: not evaluable, very-low-certainty). We did not have enough data to pool effect estimates for other outcomes.

Conclusion: Ketamine may provide small but important benefit in CNCP patients at immediate-to-short follow-up, but it probably has little to no benefit at beyond 3-weeks. Ketamine is likely to provide similar benefits compared to alternative active interventions; however, these benefits may be associated with important side-effects.

Acknowledgements

I'm deeply grateful for the support and encouragement I've received from so many wonderful people throughout this journey.

First and foremost, I would like to express my deepest appreciation to my exceptional supervisor, Dr. Behnam Sadeghirad, for endless guidance, wisdom, and patience. Your mentorship has been invaluable, and I am truly thankful for all the insights and opportunities you have provided. Your dedication to my progress, the time you invested in guiding me, and the knowledge you've shared have made a significant impact on my journey.

I would also like to acknowledge my committee members and reviewers for their expertise and invaluable contributions to this work.

To my fellow HRM students at McMaster University, thank you for your support, and friendship.

To my family, Mom, Dad, Jabe, and Nge, your unconditional love and unwavering belief in me have been my foundation, and I couldn't have done this without you. I am forever grateful and love you dearly.

And to Mohammadreza, thank you for being a source of light during my most challenging days in Canada.

Table of contents

List of Figures and Tables

List of Abbreviations

CI: confidence interval

CNS: central nervous system

CNCP: chronic non-cancer pain

CoE: certainty of evidence

CPRS: complex regional pain syndrome

GI: gastrointestinal

GRADE: grading of recommendations assessment, development, and evaluation

HRQoL: health related quality of life

IM: intramuscular

IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

IV: intravenous

MD: mean difference

MID: minimal important difference

NMA: network meta-analyses

NMDA: N-methyl-D-aspartate

NSAIDs: non-steroidal anti-inflammatory drugs

PRISMA: preferred reporting items for systematic review and meta-analyses

RCT: randomized controlled trial

RD: Risk Difference

ROB: risk of bias

RR: relative risk

SD: standard deviation

SUCRA: surface under the cumulative ranking curve

VAS: visual analogue scale

Declaration of Academic Achievement

The work described in this thesis was conducted under the leadership of Sara Moradi, referred to as the "primary researcher." The primary researcher was responsible for the study design, data collection, analysis, methodology, project management, and writing.

Dr. Behnam Sadeghirad supervised the study, provided methodological expertise, and played a significant editorial role. The committee members, Dr. Jason W. Busse and Dr. Rebecca L. Morgan, also contributed methodological expertise. Rachel Couban revised the search strategy.

Mojdeh Daneshmand, Geoff Elder, and Ahmad Sofi Mahmudi participated in screening and data extraction, under the guidance of the primary researcher. The primary researcher acted as the secondary reviewer and resolved any disagreements. The primary researcher also conducted the data analysis and interpretation and wrote the manuscript.

1. Introduction

1.1. Chronic non-cancer pain (CNCP)

CNCP, defined as pain persisting for more than three months that is not associated with a cancer diagnosis, is a prevalent and disabling condition (1). CNCP is considered as a global challenge (2). It is estimated that about one in five, or approximately 1.5 billion people, suffer from this condition (3). The prevalence of CNCP it is notably higher among vulnerable groups such as the elderly and those from diverse cultural and linguistic backgrounds, where it can rise up to 40% (4). Based on national surveys carried out between 1994 and 2008, approximately around 7 million Canadians are reported to live with CNCP, with expectations of an increase due to the aging population (5). Similarly, in the United States alone, approximately 56 million adults were reported to suffer from CNCP as of 2021 (6).

CNCP severely impacts individuals' daily lives, interfering with physical functioning. Beyond the physical domain, patients often experience substantial problems in various aspects, including psychological (anxiety, depression, and sleep disturbances), and social dimensions, which can limit a person's ability to function well, participate in society, affect work productivity and their financial well-being. These situations result in a loss of quality of life (7, 8). Certain CNCP conditions, such as chronic low back pain or chronic neck pain are among the leading causes of years lived with disability globally, contributing significantly to the overall disease burden (9).

The pathophysiology of CNCP is complex, involving different types of pain including nociceptive, neuropathic, and nociplastic (10-12). Nociceptive pain results from persistent stimulation of peripheral neurons due to tissue damage (11), while neuropathic pain arises from issues in the peripheral or central nervous system (12). Nociplastic pain results from heightened pain signals in the central

nervous system and often categorized as non-specific pain (10). Persistent pain leads to peripheral and central sensitization, where changes in the nervous system amplify pain signals (13). This sensitization causes pain modulation to be highly individual-specific. It is common for these different pain types to overlap, further complicating the clinical presentation and management of CNCP (10-12).

1.2. Economic burden

The economic burden of CNCP is substantial, impacting both healthcare systems and broader society. According to Canadian pain taskforce report, the economic burden of chronic pain was estimated to be between $38.3 and $40.4 billion in 2019 (14). This burden includes indirect costs, such as loss of productivity and disability payments, and direct healthcare costs, such as increased physician visits and longer hospital stays. For instance, individuals with CNCP in Canada have an average of 12.9 physician visits per year and longer hospital stays compared to those without chronic pain (3.8 visits and 0.7 days per year, respectively). (14). In Ontario, the incremental cost to manage chronic pain was $1,742 per patient in 2016, with hospitalization accounting for most of this expense (15).

1.3. Benefits and harms of current treatments for chronic pain

Pharmacologic interventions for management of chronic pain include opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, antiseizure medications, and infusion therapies like ketamine and lidocaine (16). The use of opioids is highly debated due to the significant risks of addiction, overdose, and death (17).

Non-opioid alternatives such as NSAIDs and tricyclic antidepressants have been found to provide similar pain relief in some cases without the severe risks associated with opioids (18), however, they often require a trial-and-error approach to find the right drug and dose (19, 20). Additionally, interventional procedures (e.g., injection of steroids and/or anesthetics) are limited to targeted pain pathologies and are not suitable for broader pain syndromes such as fibromyalgia (21). Thus, many patients continue to suffer from pain and impaired quality of life due to the limited efficacy of these pharmacologic options (22).

1.4. Ketamine

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, was first synthesized in 1962 (23). NMDA receptors are excitatory receptors found in the spinal regions, contributing to the transmission of pain signals. In cases of chronic pain, persistent stimulation results in the activation and increased expression of NMDA receptors at the dorsal horn synapses, which amplifies the pain signals transmitted to the brain. Evidence indicates that NMDA receptors antagonists, such as ketamine, can disrupt the excessive signals to the brain, offering potential alternative options for management of chronic pain (24). Ketamine's analgesic effects are primarily due to its inhibition of NMDA receptors. By blocking these receptors, it is suggested that ketamine might reduce the hyperexcitability of the central nervous system (CNS) and the amplification of pain signals, offering potential relief for chronic pain patients (24). Ketamine may also offer additional analgesic benefits by exhibiting anti-inflammatory properties (25, 26).

The use of ketamine for management of chronic pain has increased significantly over the past decade (26, 27), as it has shown promise in managing chronic pain conditions, particularly those resistant to conventional treatments (28). Conditions such as neuropathic pain (29), vascular headaches (30), and complex regional

pain syndrome (CRPS) (31) are among those suggested that ketamine administration may be associated with promising benefit and alleviating their symptoms. However, higher risk of adverse events had been reported.

1.5. Limitations of existing evidence

The existing body of research on ketamine for CNCP faces several limitations. The use of cross-over designs in numerous studies limits the ability to accurately estimate the long-term effects (32-35). Additionally, these trials often have small sample sizes and noticeable variability in treatment protocols, making it further difficult to draw definitive conclusions about the optimal dosage regimens and the long-lasting potential effects of ketamine for pain relief (36).

Systematic reviews, which aim to summarize the evidence from individual trials, also exhibit considerable limitations. Several reviews have been published on ketamine for chronic pain, yet they have been criticized for their lack of comprehensiveness and methodological rigor. For instance, the meta-analysis by Michelet et al. excluded all cross-over studies and pooled results from 195 patients only. This study did not focus on all patient-important outcomes and failed to use the minimal important difference (MID) approach while assessing the quality of evidence (36). The systematic review by Orhurhu et al. excluded trials with active control arms and pooled data from only 211 patients. This review was limited to intravenous (IV) route of administration and included cancer pain alongside CNCP, despite their different etiologies (37). Another systematic review by Zhao et al. was limited to CRPS only and included both trials and observational studies. This review did not address all patient-important outcomes. Additionally, it only evaluated publication bias and did not assess the certainty of evidence using appropriate approaches (38), The other review by Pereira et al. was more comprehensive in terms of included studies as it pooled data from 18 trials (706

patients). It and utilized appropriate tools to assess both the risk of bias and the certainty of evidence. However, this study included cancer pain alongside CNCP, despite their different aetiologies, and focused solely on pain and adverse events, neglecting other patient-important outcomes (39).

Network meta-analysis (NMA) methods allow for the use of both direct evidence and indirect evidence to assess interventions that have not been directly compared, potentially resulting in more precise summary estimates. Therefore, to address the existing gaps in our understanding of the comparative benefits and harms of ketamine for management of CNCP, we conducted a comprehensive systematic review and performed NMA to assessed relative effects of ketamine in patients diagnosed with CNCP across patient-important outcomes at different follow-up times.

Chapter 2: Methods

2.1. Standardized reporting and protocol registration

We registered our protocol with PROSPERO (CRD42022327315). We followed the preferred reporting items for systematic review and meta-analyses (PRISMA) extension statement for reporting of NMAs (40),

2.2. Data sources

A health science librarian developed database-specific search strategies, and searched MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Scopus, and the Cochrane Central Register of Controlled Trials from database inception to April 20th, 2022, which was updated on January 1st, 2024. No language restriction was applied. We reviewed reference lists from

all included trials and related reviews to identify additional eligible trials. The details of the search strategy are provided in Appendix 1.

2.3. Study selection and eligibility criteria

Reviewers received training and performed calibration exercises using standardized forms before screening for eligible studies in DistillerSR, (Evidence Partners, Ottawa, Canada, http://systematic-review.net). Pairs of reviewers independently screened the titles and abstracts identified through our searches using DistillerSR. The same reviewers independently assessed the full texts of all potentially eligible articles. Disagreements were resolved through discussion and if needed by third-party adjudication.

We included randomized controlled trials (RCTs) that: (1) enrolled adult patients (≥18 years) with CNCP (pain ≥3 months or defined by authors as “chronic”); (2) randomized patients to ketamine as a stand-alone or add-on therapy administered via any mode of delivery, or placebo, no treatment, or any type of usual care, such as oral medicines (i.e., opioids, NSAIDs, and other analgesics), and injection therapies (e.g., nerve blocks, epidural corticosteroids), and (3) measured at least one patient-important outcome recommended by the initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) statement (41). Our outcomes of interest were pain, physical function, emotional function, social function, role functioning, sleep quality, and treatment-related adverse events.

2.4. Data abstraction and risk of bias assessment

Data from eligible trials was abstracted using standardized, pilot-tested forms. Duplicate data abstraction was carried out independently by the same pairs of reviewers who performed screening for eligible studies. To ensure consistency, all reviewers completed calibration exercises with a set of 5 eligible trials. We

collected data on the following items: (i) study characteristics such as author's name, year of publication, trial design (parallel, cross-over, cluster), and country of origin; (ii) patient characteristics including mean age, proportion of female participants, type of pain (neuropathic, nociceptive, nociplastic, and mixed), and mean duration of pain; (iii) details of the intervention and comparison, including dosage, route of administration, and frequency and duration of treatment; and (iv) effects on all patient-important outcomes as listed above.

Pairs of reviewers independently evaluated the risk of bias for all eligible trials using Cochrane risk of bias tool (ROB 2.0) for parallel arm or cross-over randomized trials. This included assessing risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, risk of bias due to missing outcome data, risk of bias in measurement of the outcome, and risk of bias in selection of the reported result

Disagreements in data extraction and risk of bias assessment were resolved through discussion between the primary researcher and if needed by third-party adjudication.

2.5. Data synthesis

Individual interventions within the same medication class (e.g., NSAIDs, Opioids) were combined into a single treatment node. We did not differentiate nodes based on the dose and duration of therapy. We combined data from trial arms with different doses of ketamine using the weighted average approach recommended by the Cochrane Handbook (42). Given the variability in follow-up times for outcomes of interest (i.e., minutes vs. days vs. weeks) within or between studies, after consultation with clinical experts, we chose the following timepoints for analysis: immediate follow-up (<30 minutes), short follow-up (1-3 hours), medium follow-up (3-7 days), medium to long follow-up (3-5 weeks), and long follow-up (>5 weeks). If studies used different measurement tools capturing the same outcome,

we converted treatment effects to the most common instrument using the formulae provided by Thorlund et al (43). Specifically, we transformed pain intensity to a 10 cm visual analogue scale, and physical function to 36-item short form health survey. The MID represents the smallest improvement in a treatment outcome that patients consider significant. For the 10 cm visual analogue scale (VAS) for pain, the MID is approximately 1.5 cm (44). We used a MID of 10 points for the SF-36 physical functioning subscale (45).

We used the methods outlined by Metelli et al. to impute mean and standard deviation (SDs) when only median, interquartile range, and sample size were reported (46). For continuous outcomes, we pooled mean differences (MDs) and 95% confidence intervals (CIs), using change scores from baseline to the end of follow-up. We used change scores from baseline instead of end-of-study scores to address inter-patient variability. If change scores, standard error or the standard deviation for the differences were not reported by the authors, we imputed them using methods suggested by Cochrane handbook (42) and Hozo et al (47). For binary outcomes (adverse events) we calculated relative and absolute risks and associated 95% CIs.

We evaluated the feasibility of conducting NMA for each outcome by verifying network connectivity, ensuring that the number of trials exceeded the number of intervention nodes, confirming at least 10 trials within any network, and assessing the transitivity assumption. We considered additional rating down of each indirect comparison due to intransitivity if there were differences in the distribution of effect modifiers across the contributing direct comparisons (46). When performing NMA was feasible, we used the DerSimonian–Laird random-effects model for all direct comparisons and conducted a random-effects NMA with a common heterogeneity parameter using a frequentist approach (48, 49). For all direct comparisons, we used Cochrane's Q statistic and I^2 to evaluate statistical heterogeneity. We assessed global incoherence using design-by-treatment models (50) and local incoherence using the side-splitting approach (51). Individual interventions within

the same medication class (e.g., NSAIDs, Opioids) were combined into a single treatment node. We did not differentiate nodes based on the dose and duration of therapy. Also, for each network, we estimated ranking probabilities using the surface under the cumulative ranking curve (SUCRA) and determined the average treatment rankings. For comparisons with at least 10 trials, we evaluated small-study effects using Harbord's test for binary outcomes (52) and Egger's test for continuous outcomes (53).

When conducting NMA was not appropriate, we narratively described any available data for sleep quality and health related quality of life (HRQoL), since pooling results through meta-analysis was not suitable.

2.6. Subgroup analyses

To explore the impact of important prognostic factors on network estimates of effect, we performed subgroup analyses using NMA-regression to assess whether the efficacy and safety profile of ketamine differ based on the type of chronic pain (neuropathic, nociplastic, nociceptive, or mixed) and the overall risk of bias. Additionally, we expanded the network to evaluate different delivery methods (oral, IV, IM, intranasal, transdermal, intra-articular, and epidural) and different dosing strategy (high dose ketamine, medium dose ketamine, and low dose ketamine).

2.7. Certainty of evidence

We followed the GRADE (grading of recommendations assessment, development, and evaluation) working group's recommended approach to assess the certainty of evidence for each network estimate across different outcomes (54). Initially, we evaluated the certainty of direct estimates based on conventional GRADE guidelines (55, 56), considering limitations due to risk of bias, inconsistency, indirectness, and publication bias. Next, we assessed the certainty of indirect

estimates with a focus on the dominant lowest-order loop. Network estimates were used for assessment of precision, with the half MID as the threshold for imprecision for continuous outcomes, and null (RR=1) value as the threshold for imprecision for binary outcome. We downgraded the certainty further if unexplained incoherence between direct and indirect estimates of effect was observed.

Chapter 3: Results

3.1. Description of the evidence

We identified 3147 records through our literature search, of which full texts of 121 studies were reviewed for eligibility. We included 38 unique trials in our systematic review. Two studies failed to report any of our outcomes of interest, leaving 36 eligible trials including 1318 patients (Figure 3.1). Across the included studies, the mean age was approximately 47.8 years, with an age range spanning from 18 to 85 years. The overall percentage of female participants was 64%.

The types of chronic pain studied included neuropathic (15 studies, 41.6%), nociplastic (12 studies, 33.3%), nociceptive (6 studies, 16.6%), and mixed (3 studies, 8.5%). The mean duration of pain among the participants was 56.5 months. Of the 36 studies, 17 (47.2%) were parallel studies, and 19 (52.8%) were cross-over studies, comprising a total of 98 study arms.

The routes of administration included IV (24 studies, median dose at each injection: 0.6 mg/kg/hour, range (0.0003 to 1.8 mg/kg/hour)), epidural (4 studies, median dose at each injection 0.2 mg/kg, range (0.1 to 30 mg/kg)), oral (2 studies, median dose in each tablet 0.4 mg, range (30-50 mg)), intranasal (1 study, 10 mg in each puff), IM (2 studies, median dose not evaluable (0.2 ml, and 0.4 mg/kg)), transdermal (2 studies, median dose not evaluable (1 mg/hour and 50 mg), and

intra-articular (1 study, 0.55 mg at each injection). 27 studies (75%) were single dose administered, and 9 studies (25%) were multiple doses administered.

Regarding the source of funding, 16 studies (44.4%) were funded by non-industry sources, 14 (38.9%) had no funding statement, 3 (8.3%) explicitly stated no funding, 2 (5.6%) had a combination of industry and non-industry funding, and 1 (2.8%) was funded by the industry alone.

Geographically, the studies were distributed as follows: Sweden (7, 19.4%), USA (7, 19.4%), Netherlands (5, 13.8%), Norway (3, 8.3%), Brazil (3, 8.3%), Denmark (2, 5.6%), France (2, 5.6%), Egypt (2, 5.6%), Spain (1, 2.8%), UK (1, 2.8%), Iran (1, 2.8%), Korea (1, 2.8%), and India (1, 2.8%).

Table 3.1. provides a detailed summary of the included trial characteristics in this review.

3.2. Risk of bias (RoB)

Of the 36 trials, only 5 studies (13.9%) were at low risk of overall bias, and the majority (86.2%) had an overall high risk of bias. For the randomization process, 6 trials (16.7%) adequately generated their sequence, 2 studies (5.5%) had some concerns, and the remaining 28 trials (77.8%) were at high risk of bias. The risk of bias from carryover effects was assessed for 19 cross-over trials, with 13 studies (68.5%) at low risk, 2 studies (10.5%) with some concerns, and 4 studies (21%) at high risk. Deviations from intended interventions posed a high risk of bias in 3 studies (8.3%), 26 studies (72.2%) showed some concerns, and only 7 studies (19.5%) were at low risk of bias. For missing outcome data, 35 studies (97%) were at low risk, and only one study (3%) was at high risk. Measurement of the outcome was at low risk in 25 studies (69.5%) and at high risk in 11 studies (30.5%). Selection of the reported result was at low risk in 25 studies (69.5%), with 9 studies (25%) having some concerns and 2 studies (5.5%) at high risk. Table 3.2. provides

the details of RoB assessment across all studies with at least one outcome of interest.

3.3. Pain Intensity

3.3.1. Pain at immediate follow-up (less than 30 minutes)

Pain intensity at less than 30 minutes timepoint was reported by 15 RCTs, enrolling 633 patients. Figure 3.2 provides the network of available interventions. Of the available 11 direct comparisons, 7 comparisons were informed by 2 or more trials, and none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global or loop-specific incoherence (Table 3.3). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.4.

Low certainty evidence suggests ketamine injection may slightly reduce pain intensity (on a 0-10 VAS) compared to placebo (MD: -1.32, 95% CI: [-1.73 to -0.90], RD of patients achieving MID: 25.28, 95% CI [17.52, 32.2]), NSAIDs injection (MD: -1.56, 95% CI: [-2.42 to -0.70]), and gabapentin (MD: -1.40, 95% CI: [-2.56 to -0.24]). No other pairwise comparison showed statistically significant effect estimate (Table 3.5). Probability rankings and SUCRA values are available in Appendix Table 1.

3.3.2. Pain intensity at short follow-up (1 to 3 hours)

Pain intensity at 1 to 3 hours post-injection was reported 17 RCTs enrolling 448 patients. Figure 3.3 provides the network of available interventions. Of the available 24 direct comparisons, 8 comparisons were informed by 2 or more trials and none had important heterogeneity (I^2 = 0%). We did not find evidence of global or loop-

specific incoherence (Table 3.6). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.7.

Low certainty evidence suggests ketamine injection may reduce pain intensity compared to placebo (MD: -1.25 on a 0-10 VAS, 95% CI: [-1.76 to -0.74], RD of patients achieving MID: 23.73, 95% CI [14.64, 31.46]) and gabapentin (MD: -3.70 on a 0-10 VAS, 95% CI: [-5.12 to -2.28]). No other pairwise comparison showed statistically significant effect estimate (Table 3.8). Ranking probabilities and SUCRA values are provided in Appendix Table 2.

3.3.3. Pain intensity at medium follow-up (3 to 7 days)

Pain intensity at 3 to 7 days post-injection was reported by 14 RCTs enrolling 602 patients. Figure 3.4 provides the network of available interventions. Of the available 13 direct comparisons, only the comparison of ketamine vs placebo was informed by more than one trial (N = 6), which had substantial heterogeneity (I^2 = 70.7%). We did not find evidence of global or loop-specific incoherence (Table 3.9). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.10.

Low certainty evidence suggests ketamine injection may result in slight pain reduction compared to placebo (MD: -1.34 on a 0-10 VAS, 95% CI: [-2.29 to -0.39], RD of patients achieving MID: 24.59, 95% CI [7.8, 36.29]) and it may reduce pain intensity compared to gabapentin (MD: -3.60 on a 0-10 VAS, 95% CI: [-5.46 to -1.74]). No other pairwise comparison showed statistically significant effect estimate (Table 3.11). Ranking probabilities and SUCRA values are available in Appendix Table 3.

3.3.4. Pain intensity at medium-to-long follow-up (3 to 5 weeks)

Pain intensity at 3 to 5 weeks timepoint was reported by 11 RCTs enrolling 490 patients. Figure 3.5 provides the network of available interventions. Of the available 12 direct comparisons, only the comparison of ketamine vs placebo was informed by more than one trial (N = 4), which had moderate heterogeneity (I^2 = 49.4%). We did not find evidence of global or loop-specific incoherence (Table 3.12). Results of direct pairwise comparisons and their respective certainty of evidence are provided in table 3.13.

Moderate certainty evidence suggests ketamine injection likely have little to no effect on pain intensity compared to placebo 3 to 5 weeks post-intervention (MD: -0.99 on a 0-10 VAS, 95% CI: [-2.00 to 0.03]); however, it may reduce pain intensity compared to gabapentin (MD: -3.00 on a 0-10 VAS, 95% CI: [-4.52 to -1.48]). No other pairwise comparison showed statistically significant effect estimate (Table 3.14). Ranking probabilities and SUCRA values are available in Appendix Table 4.

3.3.5. Pain intensity at long-term follow-up (> 5 weeks)

Pain intensity at long-term follow-up was reported by 10 RCTs, enrolling 644 patients. Figure 3.6 provides the network of available interventions. Of the available 10 direct comparisons, only the comparison of ketamine vs placebo was informed by more than one trial (N = 3), which did not have important heterogeneity (I^2 = 0%). We did not find evidence of global or loop-specific incoherence (Table 3.15). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.16.

Ketamine may have little to no effect on pain intensity in time-points longer than 5 weeks post-injection, but the evidence is very uncertain: compared to placebo (MD -1.09, 95% CI: [-1.86 to -0.32], very low certainty, RD of patients achieving MID: 20.85, 95% CI [6.11, 34.08]) and compared to lidocaine (MD: -1.49, 95% CI: [-2.45 to -0.53] on a 0-10 VAS, very low certainty). Low certainty evidence suggests

ketamine injection may reduce pain intensity (on a 0-10 VAS) when compared to gabapentin (MD: -2.70, 95% CI: [-3.33 to -2.07]). No other pairwise comparison showed statistically significant effect estimate (Table 3.17). Ranking probabilities and SUCRA values are available in Appendix Table 5.

3.3.6. Additional analyses

We explored the impact of type of pain (neuropathic, nociplastic, nociceptive, mixed), and overall risk of bias on effect estimates using network meta-regression. We did not find evidence of important subgroup effect in pain reduction at any of the follow-up times (Supplementary Appendix Tables 6-27).

We explored the difference between ketamine doses and routes of administration by expanding the network of interventions. We found no statistically significant difference between high-dose, medium-dose, and low-dose ketamine injections. We also did not find any statistically significant difference between different delivery modes (Supplementary Appendix Tables 28-33).

We explored the impact of excluding stand-alone treatment nodes (midazolam, NSAIDs, and gabapentin) on the effect estimates within each network. The results indicated no statistically significant differences in the effect estimates (Supplementary Appendix Tables 34-38).

We did not have sufficient data to run subgroup analysis for the comparison of veteran vs. non-veteran population or inpatient vs. outpatient setting.

3.4. Physical function

Physical function was reported by 6 RCTs, enrolling 314 patients. We were not able to conduct analysis based on different follow-up times because of data sparsity, and thus used longest follow-up time to combine study estimates using

network meta-analysis. Figure 3.7. provides the network of available interventions. Of the available 11 direct comparisons, 2 comparisons were informed by 2 or more trials, which had substantial heterogeneity (I^2 = 85% for both). We did not find evidence of global incoherence, however loop-specific were observed between 4 comparisons (Table 3.18). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.19.

None of the ketamine pairwise comparison showed statistically significant improvement in physical function (Table 3.20). Ranking probabilities and SUCRA values are available in Appendix Table 39. We did not have sufficient data to run subgroup analysis.

3.5. Health related quality of life (HRQoL)

HRQoL was reported by two RCTs (enrolling 52 patients). Schwartzman et al. (2009) reported no statistically significant difference in placebo or ketamine injection groups at 3 months follow-up (73). Vranken et al (2005) reported a mean of 23.8-point improvement (SD: 27.09) on the 0-100 EQ-5D VAS in ketamine injection groups (combined mean of two doses), compared to a mean of 2.1-point improvement (SD: 15.96) in placebo group at 1-week of follow-up time (75).

3.6. Sleep quality

Sleep quality was evaluated by a single RCT with 20 participants. Pickering et al. (2020) observed that both ketamine alone and ketamine combined with magnesium resulted in a mean deterioration of 2 points (SD: 5.56 and 5, respectively) on the 0-21 Pittsburgh Sleep Quality Index, while the placebo group experienced a mean deterioration of 1 point (SD: 5.56) at the 5-week follow-up (72).

3.7. Social functioning

Social functioning was reported in one RCT involving 33 patients. Vranken et al. (2005) reported a mean improvement of 26.4 points (SD: 28.85) on the 0-100 SF-36 scale in the ketamine groups (combined mean of two doses), compared to a minimal 1.1-point improvement (SD: 20.88) in the placebo group at a 1-week follow-up (75).

3.8. Emotional functioning

Emotional functioning was assessed in a single RCT with 33 participants. According to Vranken et al. (2005), emotional functioning improved by a mean of 35 points (SD: 43.85) in the ketamine groups (combined mean of two doses) on the 0-100 SF-36 scale, while the placebo group showed no change (SD: 44.60) at the 1-week follow-up (75).

3.9. Role functioning

Role functioning was reported in one RCT involving 33 patients. Vranken et al. (2005) found that role functioning remained unchanged in both the ketamine groups (SD: 42.86) and the placebo group (SD: 0) at the 1-week follow-up (75).

3.10. Adverse events

3.10.1. Gastrointestinal (GI) adverse events

Almost all the included studies defined GI adverse events as nausea, vomiting, or both. GI was reported by 15 RCTs enrolling 416 patients. Figure 3.8. provides the network of available interventions. Of the available 15 direct comparisons, 5 comparisons were informed by 2 or more trials, of which none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global or

loop-specific incoherence (Table 3.21). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.22.

Ketamine injection may result in a slight increase in the risk of GI adverse events when compared to placebo (RR: 3.97, 95% CI: [2.18 to 7.22], RD: 12%, 95% CI: [5% to 25%], very low certainty). No other pairwise comparison showed statistically significant effect estimate (Table 3.23). Ranking probabilities and SUCRA values are available in Appendix Table 40.

3.10.2. Dizziness

Dizziness was reported by 12 RCTs enrolling 304 patients. Figure 3.9 provides the network of available interventions. Of the available 12 direct comparisons, 4 comparisons were informed by 2 or more trials of which none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global or loop-specific incoherence (Table 3.24). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.25.

Low certainty evidence suggests ketamine administration may increase the risk of dizziness compared to placebo (RR: 3.66, 95% CI: [1.25 to 10.74], RD: 11%, 95% CI: [1% to 40%]). No other pairwise comparison showed statistically significant effect estimate (Table 3.26). Ranking probabilities and SUCRA values are available in Appendix Table 41.

3.10.3. Fatigue, somnolence, and sedation

Fatigue, somnolence, and sedation were reported by 12 RCTs enrolling 221 patients. Figure 3.10. provides the network of available interventions. Of the available 15 direct comparisons, 5 comparisons were informed by 2 or more trials, of which none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global or loop-specific incoherence (Table 3.27). Results of

direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.28.

Low certainty evidence suggests ketamine administration may increase the risk of fatigue, somnolence, and sedation compared to placebo (RR: 2.89, 95% CI: [1.84 to 4.53], RD: 27%, 95% CI: [12% to 50%]). The evidence about comparison of ketamine administration and lidocaine is very uncertain. Ketamine administration may have little to no effect on the incidence of fatigue, somnolence, and sedation compared to lidocaine (RR: 1.38, 95% CI: [1.03 to 1.84], RD: 18%, 95%CI [1% to 40%], very low certainty), but the evidence is very uncertain. No other pairwise comparison showed statistically significant effect estimate (Table 3.29). Ranking probabilities and SUCRA values are available in Appendix Table 42.

3.10.4. Dissociative symptoms

Dissociative symptoms were reported differently amongst included trials (e.g., feeling of unreality, confusion, out of body sensation). The detailed definition of dissociative symptoms is provided in Supplementary Appendix Table 43. Dissociative symptoms were reported by 17 RCTs enrolling 482 patients. Figure 3.11. provides the network of available interventions. Of the available 15 direct comparisons, 6 comparisons were informed by 2 or more trials, of which none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global incoherence, however loop-specific were observed between 3 comparisons (Table 3.30). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.31.

Low certainty evidence suggests ketamine administration may increase the incidence of dissociative symptoms compared to placebo (RR: 4.22, 95% CI: [2.20 to 8.10], RD: 17%, 95% CI: [6% to 37%]. The evidence for the comparisons of ketamine administration and lidocaine injection and opioid injection is uncertain (for ketamine vs lidocaine, RR: 2.39, 95% CI: [1.00 to 5.68], RD: 21%, 95/5 CI [0% to 70%], and for ketamine vs opioid, RR: 2.34, 95% CI: [1.05 to 5.22], RD: 14%, 95/5

CI [1% to 45%], both very low certainty). No other pairwise comparison showed statistically significant effect estimate (Table 3.32). Ranking probabilities and SUCRA values are available in Appendix Table 44.

3.10.5. Visual impairment

Visual impairment was reported amongst included trials as blurred vision, visual disturbances, reduced visual acuity, and change in vision. Visual impairment was reported by 8 RCTs enrolling 156 patients. Figure 3.12. provides the network of available interventions. Of the available 8 direct comparisons, 5 comparisons were informed by 2 or more trials, of which none had important heterogeneity (I^2 = 0% for all comparisons). We did not find evidence of global or loop-specific incoherence (Table 3.33). Results of direct pairwise comparisons and their respective certainty of evidence are provided in Table 3.34.

The evidence about the effects of ketamine administration on visual impairment is very uncertain. Very low certainty evidence suggests ketamine administration may increase the incidence of visual impairment compared to placebo (RR: 10.21, 95% CI: [2.86 to 36.42], RD: not evaluable, very low certainty), lidocaine (RR: 5.89, 95% CI: [1.48 to 23.39], RD: 22%, 95% CI [2% to 100%]), and opioid (RR: 3.38, 95% CI: [1.03 to 11.03], RD: 17%, 95% CI [0% to 72%]). However, the evidence is very uncertain. No other pairwise comparison showed statistically significant effect estimate (Table 3.35). Ranking probabilities and SUCRA values are available in Appendix Table 45.

3.10.6. Additional analyses

We explored the impact of type of pain (neuropathic, nociceptive, nociplastic), and overall risk of bias on network estimates across adverse event outcomes using

network meta-regression and found no evidence of important subgroup effect (Supplementary Appendix Tables 46-65).

We explored the difference between Ketamine doses and route of administration by expanding the network. Medium dose ketamine administration increased the risk of dizziness compared to administration of low dose ketamine (RR: 3.77, 95% CI: [1.41 to 10.10]) (Supplementary Appendix Table 68). Additionally, IV injection of ketamine was associated with a higher risk of dizziness, when compared to transdermal injection of ketamine (RR: 37.18, 95% CI: [2.51 to 551.09]) (Supplementary Appendix Table 69). We did not find any statistically significant difference between high-dose, medium-dose, and low-dose ketamine injections in other adverse effect outcomes (Supplementary Appendix Tables 66-67, and 70-74). We also did not find any statistically significant difference between different delivery modes across other adverse effect outcomes.

We explored the impact of excluding stand-alone treatment nodes (midazolam, ketamine+midazolam, NSAIDs, and gabapentin) on the incidence of adverse events. The analysis showed no statistically significant differences in risk ratios (Supplementary Appendix Tables 75-79).

We did not have sufficient data to run subgroup analysis for the comparison of veteran vs. non-veteran population, and inpatient vs. outpatient setting.

Chapter 4: Discussion

4.1 Main findings

This NMA of 36 trials that enrolled 1,318 patients with chronic non-cancer pain showed ketamine may provide small but important pain reduction in patients with chronic pain at immediate to short-term follow-up, but it probably has little to no effect at medium to long-term (beyond 3-week post-intervention). The effect of ketamine administration on other patient-important outcomes such as physical

functioning, quality of life and sleep, and social and emotional function is very uncertain. Ketamine administration may have some benefit in pain reduction compared to gabapentin across all follow-ups, NSAIDs at immediate follow-up, and lidocaine at the long-term follow-up. Low to very low certainty evidence indicates that ketamine may be associated with an increased risk of all adverse effects. Compared to lidocaine and opioid, very low certainty evidence suggests ketamine may be associate with higher incidence of fatigue, somnolence and sedation, dissociative symptoms, and visual impairment.

4.2 Strengths and limitations

Our study, which is the first NMA to evaluate the comparative effectiveness and safety of ketamine across various types of CNCP, has several notable strengths. We conducted a systematic review and network meta-analysis, guided by a detailed and publicly available study protocol, to ensure transparency and rigor. The search strategy was comprehensive and was developed in collaboration with an experienced health sciences librarian. We utilized advanced statistical methods, including network meta-regression and network expanding to explore the impact of potential effect modifiers and ensure robustness in our findings. Additionally, we employed the minimally contextualised GRADE approach to evaluate the certainty of evidence, to provide a clear and transparent presentation of ketamine's comparative performance.

However, some limitations of our work need to be mentioned. The primary limitation of our review is the low certainty of evidence, largely due to trial limitations, including high risk of bias and the small number of patients included in each trial, making imprecision a significant limiting factor in the quality of the evidence produced. Also, our review could not assess long-term benefits and harms of ketamine for CNCP, because none of the included trials in the analysis trial followed patients for more than 6 months.

4.3 Comparison with other reviews

Our findings align with those reported in previous systematic reviews on ketamine for CNCP. Consistent with earlier reviews, our analysis found that ketamine provides modest pain relief when compared to placebo, however the existing evidence remain low in most cases. Additionally, the magnitude of pain relief does not significantly change with different ketamine doses (36-39). Previous reviews also highlighted the higher incidence of adverse events, particularly dissociative symptoms, associated with ketamine, which our study confirms (36-39). We were unable to compare other outcomes with previous reviews, as these were not analyzed in earlier studies.

4.4 Implications for practice and research

The findings of this study have important implications for clinical practice and future research. The absence of regulatory guidance on optimal dosing regimens, yielding to significant variability in ketamine dosing and administration methods, raises concerns about the potential risks associated with ketamine treatments (91, 92). Therefore, there is a clear need for comprehensive research and clear clinical guidelines. Moreover, the lack of consistent reporting of important patient-reported outcomes, as recommended by IMMPACT, highlights an area for improvement in future trials (41). Given the small number of patients included in many of the studies, there is a clear need for larger, definitive RCTs to further evaluate ketamine's efficacy and safety.

4.5 Conclusion

In conclusion, this systematic review and meta-analysis provide a comprehensive evaluation of ketamine's role in managing chronic non-cancer pain (CNCP). Our findings suggest that ketamine may offer small but meaningful benefits in patients

with chronic pain at immediate to short-term follow-up, though it likely provides little to no benefit at medium to long-term follow-up (beyond three weeks post-intervention). Additionally, while ketamine may offer similar benefits compared to other active interventions, these potential advantages are often accompanied by significant adverse effects. These findings highlights the need for further research to establish standardized dosing regimens and long-term safety profiles of ketamine.

Figure 3.1. Flow diagram of the study selection process

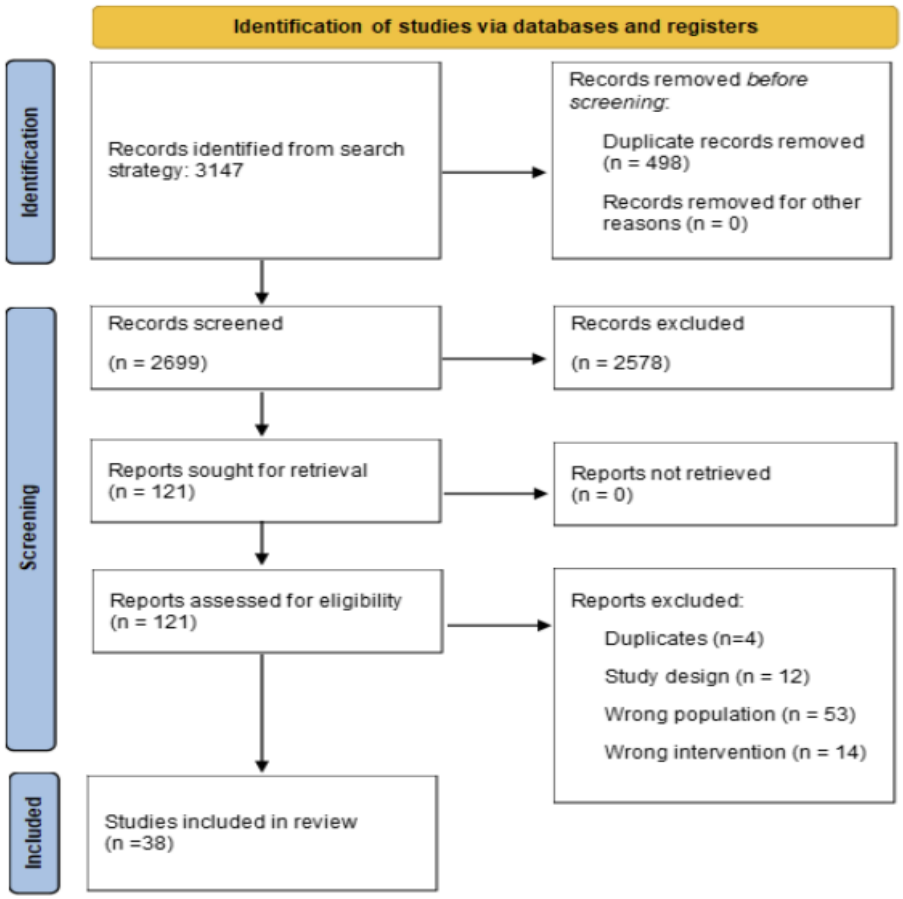


Table 3.1 Characteristics of included trials

Authors	Country	Mean age	% Female	Pain type	Pain duration (month)	RCT type	# Arms	Ketamine dose at each use	Route of administration	Frequency
Collazo 2015 (57)	Spain	51	93	Nociplastic	88.8	Parallel	3*	0.4 mg/kg/h	IV	5 days, each day 1 hour
Jørum 2002 (32)	Norway	47.5	58.3	Neuropathic	81.99	Cross-over	3	0.018 mg/kg/h	IV	Once for 20 minutes
Kvarnstorm 2004 (58)	Sweden	44.9	10	Neuropathic	99.6	Cross-over	3	0.6 mg/kg/h	IV	Once for 40 minutes
Kvarnstorm 2003 (59)	Sweden	46.75	75	Neuropathic	69.5	Cross-over	3	0.6 mg/kg/h	IV	Once for 40 minutes
Lemming 2005 (60)	Sweden	41	69.69	Nociplastic	28	Cross-over	4	0.6 mg/kg/h	IV	Once for 30 minutes
Lemming 2007 (61)	Sweden	34.1	55	Nociplastic	45.8	Cross-over	4	0.0003 mg/kg/h	IV	Once for 65 minutes
Lumanauw 2019 (62)	USA	46.5	58.7	Mixed	NR**	Parallel	3	0.75 mg/kg/h	IV	Once for 20 minutes
Maher 2017 (63)	USA	50.26	54.09	Nociceptive	NR**	Parallel	2*	1 mg/kg/h	IV	Once for 30 minutes

Carr 2004 (64)	USA	48.55	70	Mixed	NR**	Cross-over	2	10 mg	Intranasal	Once for 60 minutes
Castrillon 2008 (65)	Denmark	28.01	71.4	Nociplastic	96	Cross-over	2	0.2 ml	IM	Once for 10 second
Dadabayev 2020 (66)	USA	45.44	24.3	Mixed	NR**	Parallel	4	0.75 mg/kg/h	IV	Once for 40 minutes
Lauretti 2009 (67)	Brazil	45.82	72	Nociceptive	88.32	Parallel	6	NE ***	Transdermal	Once for 360 minutes
Max 1995 (68)	USA	40	100	Nociplastic	46.5	Cross-over	3	0.75 mg/kg/h	IV	120 minutes daily for 3 days
Mitchell 2002 (69)	UK	71	43	Nociceptive	23.2	Parallel	2	0.15 mg/kg/h	IV	Once for 240 minutes
Muller 2005 (70)	France	42.05	100	Nociplastic	NR**	Cross-over	2	0.0416 mg/kg/h	IV	Continuous infusion for 60 hours
Niesters 2013 (71)	Netherlands	54.4	80	Neuropathic	NR**	Cross-over	3	0.57 mg/kg/h	IV	Once for 60 minutes
Pickering 2020 (72)	France	55	50	Neuropathic	60	Cross-over	3	0.25 mg/kg/h	IV	Once for 120 minutes
Schwartzman 2009 (73)	USA	41.9	95	Nociplastic	79.6	Parallel	2	0.35 mg/kg/hour	IV	240 minutes daily for 10 days

Sigtermans 2009 (74)	Netherlands	45.6	80	Nociplastic	93.6	Parallel	2	0.432 mg/kg/h	IV	3 times daily for 5 days
Sorensen 1995 (33)	Sweden	39	100	Nociplastic	117.84	Cross-over	2	1.8 mg/kg/h	IV	Once for 10 minutes
Sorensen 1997 (34)	Sweden	39	100	Nociplastic	60	Cross-over	4	0.6 mg/kg/h	IV	Once for 30 minutes
Vranken 2005 (75)	Netherlands	53.8	52	Neuropathic	NR**	Parallel	3	NE ***	Transdermal	daily for 5 days
Noppers 2011 (76)	Netherlands	42.1	96	Nociplastic	57.6	Parallel	2	1 mg/kg/h	IV	Once for 30 minutes
Persson 1998 (77)	Sweden	72.7	63	Nociceptive	NR**	Cross-over	4	1.8 mg/kg/h	IV	Once for 5 minutes
Ayesh 2008 (35)	Denmark	26.5	83	Nociceptive	50.4	Cross-over	2	NE ***	Intra-articular	Once
Amr B 2011 (78)	Egypt	30.90	15	Neuropathic	8.5	Parallel	2	0.2 mg/kg	Epidural	Once
Jafarnia 2016 (79)	Iran	39.82	75	Nociceptive	NR**	Parallel	2	50 mg	Oral	Three times daily for 6 weeks
Lauretti 2002 (80)	Brazil	46.6	39	Neuropathic	NR**	Parallel	2	0.1 mg/kg	Epidural	Once weekly for 3 weeks
Rigo 2017 (81)	Brazil	50.14	54	Neuropathic	12	Parallel	3	30 mg	Oral	3 times daily

Kim 2015 (82)	Korea	69	70	Neuropathic	21	Parallel	2	1 mg/kg/h	IV	60 minutes, every other day for one week
Amr A 2011 (83)	Egypt	44.9	45.4	Neuropathic	9.5	Parallel	2	30 mg	Epidural	Once
Peter 2023 (84)	India	NR	15	Neuropathic	NR**	Parallel	2	0.2 mg/kg	Epidural	Once
Leung 2001 (85)	USA	55.8	41.6	Neuropathic	71.08	Cross-over	3	NE ***	IV	Once for 20 minutes
Bouwense 2011 (86)	Netherlands	53.2	55	Nociplastic	NR**	Cross-over	2	0.12 mg/kg/h	IV	Once for 180 minutes
Eide 1994 (87)	Norway	71.87	50	Neuropathic	42.5	Cross-over	3	0.9 mg/kg/h	IV	Once for 10 minutes
Rabben 1999 (88)	Norway	56.86	87	Neuropathic	5.7	Cross-over	2	0.4 mg/kg	IM	Once
Nielsen 2000**** (89)	Sweden	45	100	Nociplastic	44.4	Cross-over	2	0.6 mg/kg/h	IV	Once for 30 minutes
Haines 1999 **** (90)	UK	NR	50	Neuropathic	120	Cross-over	2	10 mg	Oral	Once daily for 3 weeks

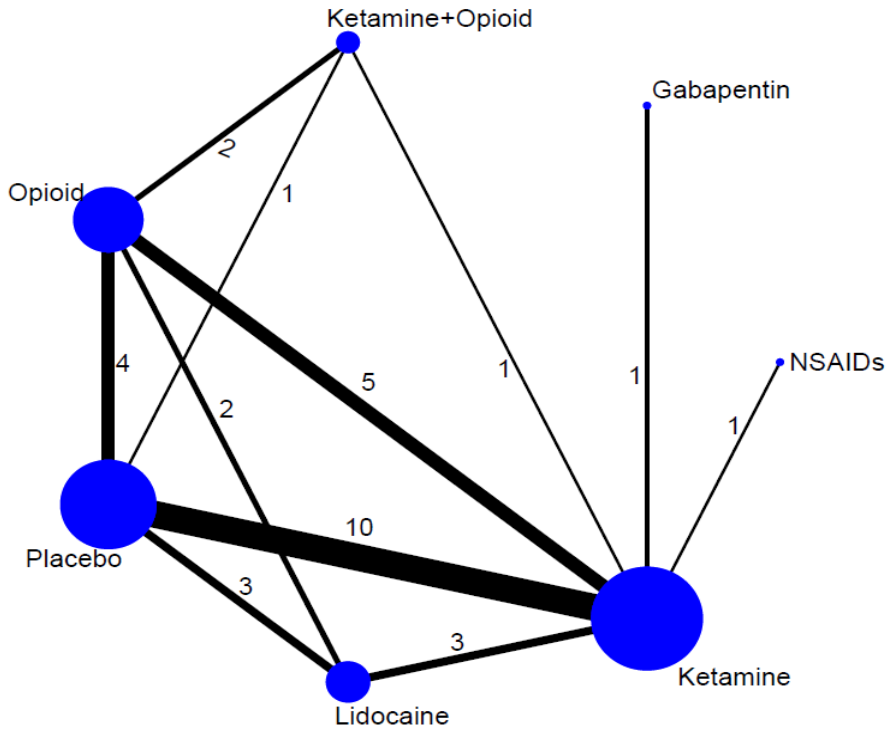
* Studies had more arms, but only 3 and 2 arms were eligible to be included, ** Mean duration of pain not reported; however, it was explicitly mentioned to be chronic pain, *** Mean Ketamine at dose at each was not evaluable, **** Studies were not included in the analysis. IV: intra-venous, IM: intramuscular

Table 3.2. Risk of bias assessment across all studies with at least one outcome of interest.

Study (year)	Randomization Process	Carryover Effects	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Jørum 2002 (32)	Some concerns	Some concerns	High	Low	Low	Some concerns	High
Kvarnstorm 2003 (59)	High	Low	Some concerns	Low	Low	Low	High
Lemming 2005 (60)	High	Low	High	Low	Low	Some concerns	High
Lemming 2007 (61)	High	Low	Low	Low	Low	Some concerns	High
Lumanauw 2019 (62)	Low	Not Applicable	Low	Low	Low	Low	Low
Maher 2017 (63)	High	Not Applicable	Low	Low	Low	Low	High
Carr 2004 (64)	Low	High	Low	Low	Low	Low	Low
Castrillon 2008 (65)	High	Low	Some concerns	Low	Low	Some concerns	High
Dadabayev 2020 (66)	High	Not Applicable	Some concerns	Low	Low	High	High
Sorensen 1995 (33)	High	Some concerns	Some concerns	Low	High	Some concerns	High
Sorensen 1997 (34)	High	Low	Some concerns	Low	High	Low	High
Persson 1998 (77)	Some concerns	High	Some concerns	Low	High	Low	High
Ayesh 2008 (35)	High	Low	Some concerns	Low	High	High	High
Amr [A] 2011 (83)	High	Not Applicable	Some concerns	High	Low	Low	High
Amr [B] 2011 (78)	High	Not Applicable	Some concerns	Low	High	Low	High
Peter 2023 (84)	High	Not Applicable	Some concerns	Low	Low	Low	High
Kvarnstorm 2004 (58)	High	High	Some concerns	Low	Low	Low	High
Lauretti 2009 (67)	High	Not Applicable	Some concerns	Low	Low	Low	High
Max 1995 (68)	High	High	Some concerns	Low	High	Some concerns	High
Niesters 2013 (71)	High	Low	Some concerns	Low	High	Low	High
Noppers 2001 (76)	Low	Not Applicable	Low	Low	Low	Low	Low
Mitchell 2002 (69)	High	Not Applicable	Some concerns	Low	High	Some concerns	High
Muller 2005 (70)	High	Low	Some concerns	Low	High	Low	High
Schwartzman 2009 (73)	High	Not Applicable	Some concerns	Low	Low	Some concerns	High

Sigtermans 2009 (74)	High	Not Applicable	Some concerns	Low	Low	Low	High
Vranken 2005 (75)	High	Not Applicable	Some concerns	Low	Low	Low	High
Jafarnia 2016 (79)	Low	Not Applicable	Low	Low	Low	Low	Low
Lauretti 2002 (80)	High	Not Applicable	Some concerns	Low	Low	Low	High
Rigo 2017 (81)	High	Not Applicable	Some concerns	Low	Low	Low	High
Kim 2015 (82)	High	Not Applicable	Some concerns	Low	Low	Low	High
Collazo 2015 (57)	Low	Not Applicable	High	Low	Low	Some concerns	High
Pickering 2020 (72)	Low	Low	Low	Low	Low	Low	Low
Leung 2001 (85)	High	Low	Some concerns	Low	Low	Low	High
Bouwense 2011 (86)	High	Low	Some concerns	Low	High	Low	High
Eide 1994 (87)	High	Low	Some concerns	Low	High	Low	High
Rabben 1999 (88)	High	Low	Some concerns	Low	Low	Low	High

Figure 3.2. Network map of pain intensity at immediate follow-up



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.3. Indirect estimates of effect for the network of pain intensity at immediate follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs. Placebo	-1.88 (-5.29, 1.53)	0.58 (1.76)	0.743
Ketamine vs. Ketamine+Opioid	1.56 (0.12, 2.99)	-1.36 (1.07)	0.205
Ketamine vs. Lidocaine	-0.93 (-2.42, 0.56)	0.62 (0.84)	0.461
Ketamine vs. Opioid	-0.64 (-2.09, 0.80)	0.53 (0.82)	0.520
Ketamine+Opioid vs. Placebo	-2.82 (-4.26, -1.37)	1.21 (1.06)	0.256
Ketamine+Opioid vs. Opioid	0.23 (-2.27, 2.74)	-1.65 (1.40)	0.241
Lidocaine vs. Placebo	-1.23 (-2.77, 0.32)	0.39 (0.85)	0.647
Lidocaine vs. Opioid	-0.06 (-1.24, 1.12)	0.44 (0.78)	0.572
Opioid vs. Placebo	-0.99 (-2.19, 0.20)	-0.15 (0.71)	0.834

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.988

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.4. Results of direct pairwise comparisons with number of trials and certainty of evidence for pain intensity at immediate follow-up

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. NSAIDs	1	39	--	-1.56 (-2.02,-1.10)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Gabapentin	1	40	--	-1.40 (-2.30, -0.5)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Opioid	1	40	--	0.2 (-1.15, 1.55)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Opioid	5	198	0	-0.07 (-0.98, 0.84)	Serious	Not serious	Serious	Serious	Undetected	Very Low
Ketamine vs. Placebo	10	434	0	-1.29 (-1.77,-0.81)	Not serious	Not serious	Not serious	Very serious	Not serious*	Low
Ketamine vs. Lidocaine	3	126	0	-0.30 (-0.9, 0.311)	Serious	Not serious	Serious	Serious	Undetected	Very Low
Ketamine+Opioid vs. Opioid	2	80	0	-1.41 (-2.62,-0.21)	Very serious	Not serious	Not serious	Not serious	Undetected	Mode rate
Ketamine+Opioid vs. Placebo	1	40	--	-1.60 (-2.92,-0.28)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Opioid vs. Placebo	4	166	0	-1.17 (-1.75,-0.60)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Lidocaine vs. Opioid	2	102	0	0.42 (-0.69, 1.50)	Serious	Not serious	Serious	Serious	Undetected	Very Low
Lidocaine vs. Placebo	3	126	0	-0.91 (-1.31,-0.51)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence
* Egger test p value: 0.218

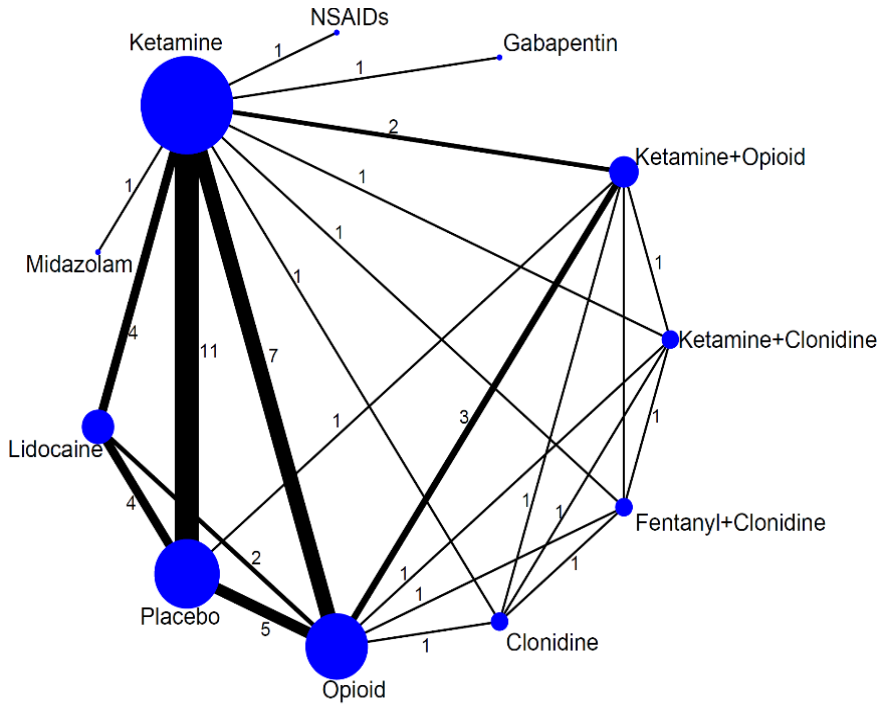
Table 3.5. Results of network meta-analysis with GRADE certainty of evidence for pain reduction at immediate follow-up time

Ketamine						
0.92 (-0.13,1.97)	Ketamine+Opioid					
-0.41 (-1.00,0.17)	-1.34 (-2.48,-0.20)	Lidocaine				
-1.56 (-2.42,-0.70)	-2.48 (-3.84,-1.13)	-1.15 (-2.19,-0.10)	NSAID			
-1.40 (-2.56,-0.24)	-2.32 (-3.89,-0.76)	-0.99 (-2.29,0.31)	0.16 (-1.29,1.61)	Gabapentin		
-0.22 (-0.80,0.37)	-1.14 (-2.14,-0.14)	0.20 (-0.52,0.91)	1.34 (0.30,2.39)	1.18 (-0.12,2.49)	Opioid	
-1.32 (-1.73,-0.90)	-2.24 (-3.29,-1.19)	-0.90 (-1.48,-0.33)	0.24 (-0.72,1.20)	0.08 (-1.15,1.32)	-1.10 (-1.69,-0.51)	Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.3. Network map of pain intensity at short follow-up



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.6. Indirect estimates of effect for the network of pain intensity at short follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Clonidine vs. Ketamine	-1.85 (-5.33, 1.63)	1.75 (1.81)	0.333
Clonidine vs. Ketamine+Opioid	0.82 (-2.99, 4.62)	-0.72 (2.37)	0.763
Clonidine vs. Opioid	0.68 (-2.57, 3.94)	-1.68 (2.06)	0.413
Fentanyl+Clonidine vs. Ketamine	-2.25 (-5.69, 1.19)	1.75 (1.81)	0.333
Fentanyl+Clonidine vs. Ketamine+Opioid	0.42 (-3.35, 4.18)	-0.72 (2.37)	0.763
Fentanyl+Clonidine vs. Opioid	0.28 (-2.93, 3.49)	-1.68 (2.06)	0.413
Ketamine+Clonidine vs. Ketamine	-0.95 (-4.50, 2.60)	1.75 (1.81)	0.333
Ketamine+Clonidine vs. Ketamine+Opioid	1.72 (-2.15, 5.59)	-0.72 (2.37)	0.763
Ketamine+Clonidine vs. Opioid	1.58 (-1.75, 4.91)	-1.68 (2.06)	0.413
Ketamine vs. Placebo	-2.96 (-5.70, -0.22)	1.77 (1.42)	0.213
Ketamine vs. Ketamine+Opioid	1.43 (-0.08, 2.94)	-1.17 (0.99)	0.237
Ketamine vs. Lidocaine	-1.74 (-3.14, -0.34)	1.77 (0.78)	0.022
Ketamine vs. Opioid	0.48 (-1.10, 2.06)	-0.58 (0.88)	0.509
Ketamine+Opioid vs. Placebo	-2.24 (-3.59, -0.89)	0.65 (1.11)	0.562
Ketamine+Opioid vs. Opioid	0.44 (-1.90, 2.79)	-1.42 (1.31)	0.279
Lidocaine vs. Placebo	-1.10 (-2.88, 0.69)	0.21 (1.02)	0.839
Lidocaine vs. Opioid	-0.23 (-1.36, 0.90)	1.02 (0.79)	0.196
Opioid vs. Placebo	-0.19 (-1.28, 0.89)	-1.54 (0.67)	0.022

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.235

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency. IF: inconsistency factor; Se: standard error

Table 3.7. Results of direct pairwise comparisons with number of trials and certainty of evidence for pain reduction at short follow-up

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. NSAID	1	39	--	-0.57 (-1.05, -0.09)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Gabapentin	1	40	--	-3.70 (-4.67, -2.73)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Ketamine+Opioid	2	58	0	0.33 (-0.73, 1.40)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Clonidine	1	17	--	-0.80 (-2.65, 1.05)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Fentanyl+Clonidine	1	16	--	0.50 (-1.12, 2.12)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Clonidine	1	18	--	0.10 (-1.61, 1.81)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Opioid	7	225	0	-0.17 (-1.09, 0.75)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs. Placebo	11	403	0	-1.25 (-1.77, -0.74)	Not serious	Not serious	Not serious	Not serious	Not serious*	High
Ketamine vs. Lidocaine	4	146	0	0.07 (-0.39, 0.53)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs. Midazolam	1	24	--	-0.91 (-2.76, 0.94)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine+Opioid vs. Ketamine+Clonidine	1	17	--	-1.00 (-3.37, 1.37)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Opioid vs. Fentanyl+Clonidine	1	16	--	0.30 (-1.90, 2.50)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Opioid vs. Clonidine	1	18	--	-0.10 (-2.36, 2.16)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Opioid vs. Opioid	3	97	0	-0.96 (-1.84, -0.09)	Very serious	Not serious	Serious	Not serious	Undetected	Very Low
Ketamine+Opioid vs. Placebo	1	40	--	-1.60 (-2.91, -0.29)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Clonidine vs. Fentanyl+Clonidine	1	15	--	1.30 (-0.91, 3.51)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

Ketamine+Clonidine vs. Clonidine	1	17	--	0.90 (-1.37, 3.17)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Clonidine vs. Opioid	1	16	--	-0.10 (-2.37, 2.17)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Fentanyl+Clonidine vs. Clonidine	1	16	--	-0.40 (-2.49, 1.69)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Fentanyl+Clonidine vs. Opioid	1	15	--	-1.40 (-3.49, 0.69)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Clonidine vs. Opioid	1	17	--	-1.00 (-3.16, 1.16)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Opioid vs. Placebo	5	176	0	-1.54 (-2.16, -0.92	Serious	Not serious	Not serious	Serious	Undetected	Low
Opioid vs. Lidocaine	2	102	0	-0.84 (-2.06, 0.38)	Very serious	Not serious	Serious	Serious	Undetected	Very Low
Lidocaine vs. Placebo	4	146	0	-0.90 (-1.32, -0.48)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low

CoE: certainty of evidence

* Egger test p value: 0.413

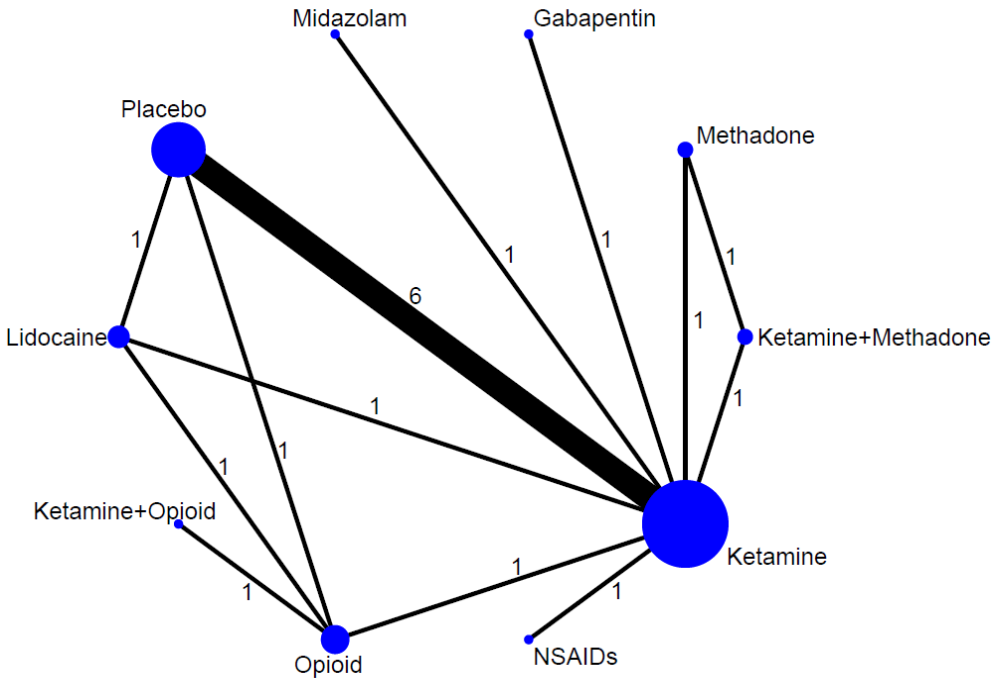
Table 3.8. Results of network meta-analysis with certainty of evidence for pain reduction at short follow-up time

Ketamine									
0.41 (-1.49,2.31)	Clonidine								
0.81 (-1.01,2.63)	0.40 (-1.94,2.74)	Fentanyl+Clonidine							
-3.70 (-5.12,-2.28)	-4.11 (-6.48,-1.74)	-4.51 (-6.82,-2.20	Gabapentin						
-0.49 (-2.51,1.53)	-0.90 (-3.40,1.60)	-1.30 (-3.74,1.14)	3.21 (0.74,5.68)	Ketamine+Clonidine					
0.74 (-0.27,1.74)	0.33 (-1.70,2.36)	-0.07 (-2.03,1.89)	4.44 (2.70,6.18)	1.23 (-0.92,3.38)	Ketamine+Opioid				
-0.32 (-0.98,0.35)	-0.73 (-2.72,1.27)	-1.13 (-3.05,0.79)	3.38 (1.82,4.95)	0.17 (-1.94,2.29)	-1.06 (-2.19,0.08)	Lidocaine			
-0.91 (-3.03,1.21)	-1.32 (-4.17,1.52)	-1.72 (-4.51,1.07)	2.79 (0.24,5.34)	-0.42 (-3.35,2.51)	-1.65 (-3.99,0.70)	-0.59 (-2.81,1.63)	Midazolam		
-0.57 (-1.71,0.57)	-0.98 (-3.20,1.23)	-1.38 (-3.53,0.77)	3.13 (1.31,4.95)	-0.08 (-2.40,2.24)	-1.31 (-2.83,0.21)	-0.25 (-1.57,1.07)	0.34 (-2.07,2.75)	NSAIDs	
0.00 (-0.63,0.63)	-0.41 (-2.35,1.52)	-0.81 (-2.67,1.05)	3.70 (2.15,5.25)	0.49 (-1.57,2.55)	-0.74 (-1.72,0.24)	0.32 (-0.45,1.09)	0.91 (-1.30,3.12)	0.57 (-0.73,1.87	Opioid
-1.25 (-1.76,-0.74)	-1.66 (-3.61,0.29)	-2.06 (-3.93,-0.19	2.45 (0.94,3.96)	-0.76 (-2.83,1.31)	-1.99 (-3.03,-0.95	-0.93 (-1.60,-0.26	-0.34 (-2.52,1.84)	-0.68 (-1.93,0.57	-1.25 (-1.91,-0.59)	Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.4. Network map of pain intensity at medium follow-up



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.9. Indirect estimates of effect for the network of pain intensity at medium follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs. Lidocaine	-2.01 (-6.35, 2.34)	1.61 (2.47)	0.515
Ketamine vs. Opioid	-1.91 (-6.24, 2.43)	1.61 (2.47)	0.515
Lidocaine vs. Placebo	-1.91 (-6.25, 2.44)	1.61 (2.47)	0.515
Opioid vs. Placebo	-2.01 (-6.34, 2.33)	1.61 (2.47)	0.515

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.515

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.10. Results of direct pairwise comparisons with number of trials and certainty of evidence for pain reduction at medium follow-up

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. Ketamine+Methadone	1	40	--	0.83 (0.14, 1.52)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Methadone	1	24	--	0.81 (-0.01, 1.63)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Gabapentin	1	40	--	-3.60 (-4.07, -3.13)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Midazolam	1	24	--	-0.85 (-2.55, 0.85)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Placebo	6	240	70.7	-1.32 (-2.36, -0.29)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs. Lidocaine	1	66	--	-0.40 (-1.38, 0.58)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Opioid	1	66	--	-0.30 (-1.23, 0.63)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. NSAID	1	39	--	-0.38 (-0.78, 0.02)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine+Methadone vs. Methadone	1	26	--	-0.02 (-0.88, 0.84)	Serious	Not serious	Not serious	Serious	Undetected	Low
Opioid vs. Placebo	1	66	--	-0.40 (-1.33, 0.53)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs. Opioid	1	66	--	0.10 (-0.87, 1.07)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs. Placebo	1	66	--	-0.30 (-1.28, 0.68)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine+Opioid vs. Opioid	1	28	--	-1.27 (-2.90, 0.36)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence

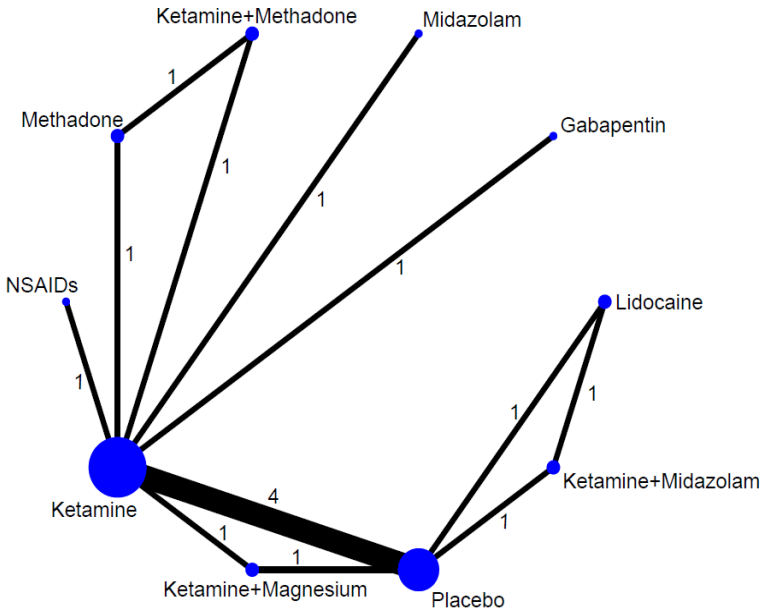
Table 3.11. Results of network meta-analysis with certainty of evidence for pain reduction at medium follow-up time

Ketamine								
0.65 (-2.39,3.69)	Ketamine+Opioid							
-0.72 (-2.56,1.12)	-1.37 (-4.55,1.81)	Lidocaine						
-0.38 (-2.23,1.47)	-1.03 (-4.58,2.53)	0.34 (-2.27,2.95)	NSAIDs					
-3.60 (-5.46,-1.74)	-4.25 (-7.81,-0.69)	-2.88 (-5.50,-0.26)	-3.22 (-5.84,-0.60)	Gabapentin				
-0.62 (-2.44,1.20)	-1.27 (-3.70,1.16)	0.10 (-1.95,2.15)	-0.24 (-2.83,2.35)	2.98 (0.38,5.58)	Opioid			
-0.85 (-3.33,1.63)	-1.50 (-5.42,2.42)	-0.13 (-3.22,2.96)	-0.47 (-3.56,2.62)	2.75 (-0.35,5.85)	-0.23 (-3.31,2.85)	Midazolam		
0.83 (-1.10,2.76)	0.18 (-3.42,3.78)	1.55 (-1.12,4.22)	1.21 (-1.46,3.88)	4.43 (1.75,7.11)	1.45 (-1.20,4.10)	1.68 (-1.46,4.82)	Ketamine+Methadone	
0.81 (-1.17,2.79)	0.16 (-3.47,3.79)	1.53 (-1.18,4.24)	1.19 (-1.52,3.90)	4.41 (1.69,7.13)	1.43 (-1.26,4.12)	1.66 (-1.52,4.84)	-0.02 (-2.02,1.98)	Methadone
-1.34 (-2.29,-0.39)	-1.99 (-5.03,1.05)	-0.62 (-2.46,1.22)	-0.96 (-3.04,1.12)	2.26 (0.17,4.35)	-0.72 (-2.54,1.10)	-0.49 (-3.15,2.17)	-2.17 (-4.32,-0.02)	-2.15 (-4.35,0.05)	Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.5. Network map of pain intensity at medium-to-long follow-up



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.12. Indirect estimates of effect for the network of pain intensity at medium-to-long follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs. Ketamine+Magnesium	-2.65 (-6.41, 1.11)	2.65 (2.22)	0.232
Ketamine+Magnesium vs. Placebo	-2.65 (-6.63, 1.34)	2.65 (2.22)	0.232

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.232

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.13. Results of direct pairwise comparisons with number of trials and certainty of evidence for pain reduction at medium-to-long follow-up

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. NSAID	1	40	--	-0.21 (-2.49, 2.07)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs. Methadone	1	24	--	0.85 (-0.03, 1.73)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Methadone	1	24	--	0.53 (-0.27, 1.33)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Midazolam	1	24	--	0.68 (-1.17, 2.53)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs. Gabapentin	1	40	--	-3.00 (-3.57, -2.43)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs. Placebo	4	159	49.7	-0.99 (-1.99, 0.02)	Very serious	Not serious	Serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Magnesium	1	40	--	0.00 (-1.45, 1.45)	Serious	Not serious	Not serious	Not serious	Undetected	Moderate
Methadone vs. Ketamine+Methadone	1	26	--	-0.32 (-1.16, 0.52)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine+Midazolam vs. Lidocaine	1	91	--	-0.90 (-1.54, -0.26)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs. Placebo	1	89	--	0.00 (-0.62, 0.62)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine+Midazolam vs. Placebo	1	91	--	-0.90 (-1.54, -0.26)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs. Placebo	1	40	--	0.00 (-1.24, 1.24)	Serious	Not serious	Not serious	Not serious	Undetected	Moderate

CoE: certainty of evidence

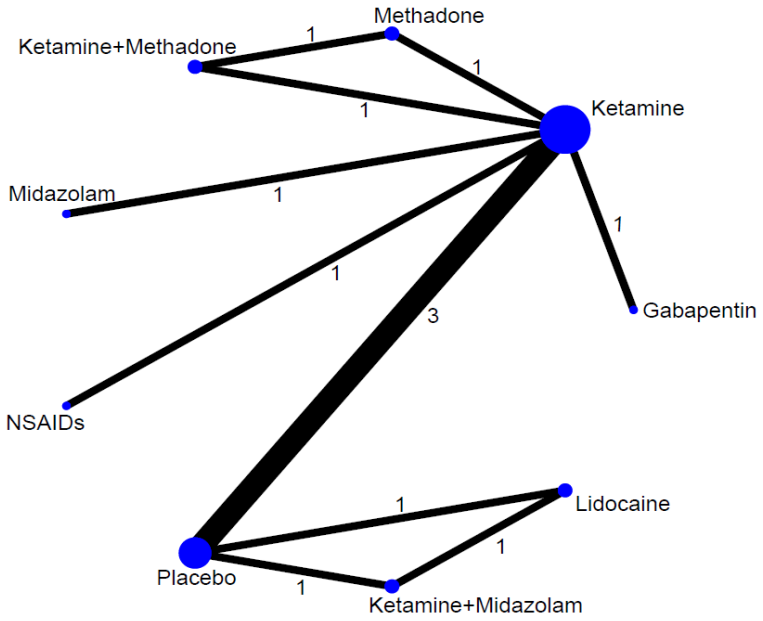
Table 3.14. Results of network meta-analysis with certainty of evidence for pain reduction at medium-to-long follow-up time

Ketamine								
-3.00 (-4.52,-1.48)	Gabapentin							
-0.09 (-1.94,1.77)	2.91 (0.52,5.31)	Ketamine+Midazolam						
-0.56 (-2.33,1.21)	2.44 (0.10,4.77)	-0.48 (-2.79,1.84)	Ketamine+Magnesium					
0.53 (-1.09,2.15)	3.53 (1.30,5.76)	0.62 (-1.85,3.08)	1.09 (-1.31,3.49)	Ketamine+Methadone				
-0.99 (-2.83,0.86)	2.01 (-0.38,4.41)	-0.90 (-2.45,0.65)	-0.42 (-2.74,1.89)	-1.52 (-3.98,0.94)	Lidocaine			
0.85 (-0.81,2.51)	3.85 (1.60,6.10)	0.94 (-1.55,3.42)	1.41 (-1.02,3.84)	0.32 (-1.32,1.96)	1.84 (-0.65,4.32)	Methadone		
0.68 (-1.65,3.01)	3.68 (0.90,6.46)	0.77 (-2.21,3.74)	1.24 (-1.68,4.17)	0.15 (-2.69,2.99)	1.67 (-1.31,4.64)	-0.17 (-3.03,2.69)	Midazolam	
-0.21 (-2.89,2.47)	2.79 (-0.29,5.87)	-0.12 (-3.38,3.13)	0.35 (-2.86,3.56)	-0.74 (-3.87,2.39)	0.78 (-2.48,4.03)	-1.06 (-4.21,2.09)	-0.89 (-4.44,2.66)	NSAIDs
-0.99 (-2.00,0.03)	2.01 (0.18,3.84)	-0.90 (-2.45,0.65)	-0.42 (-2.15,1.30)	-1.52 (-3.43,0.40)	0.00 (-1.54,1.54)	-1.84 (-3.78,0.11)	-1.67 (-4.21,0.87)	-0.78 (-3.64,2.09)	Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.6. Network map of pain intensity at long-term follow-up



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.15. Indirect estimates of effect for the network of pain intensity at long-term follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Ketamine+Methadone vs. Methadone	0.57 (-1.88, 3.02)	-0.17 (0)	.

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = -- (data contain no potential source of inconsistency)

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.16. Results of direct pairwise comparisons with number of trials and certainty of evidence for pain reduction at long-term follow-up

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. Methadone	1	24	--	0.50 (-2.33, 3.33)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Methadone	1	24	--	0.10 (-2.98, 3.18)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Midazolam	1	24	--	1.13 (-1.08, 3.34)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs. NSAID	1	40	--	0.28 (-3.07, 3.63)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs. Placebo	3	119	0	-1.09 (-1.86, -0.32)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs. Gabapentin	1	40	--	-2.70 (-3.33, -2.07)	Serious	Not serious	Not serious	Serious	Undetected	Low
Methadone vs. Ketamine+Methadone	1	26	--	-0.40 (-2.80, 2.00)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Midazolam vs. Placebo	1	90	--	-1.10 (-1.71, -0.49)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Lidocaine vs. Placebo	1	89	--	0.40 (-0.17, 0.97)	Serious	Not serious	Not serious	Not serious	Undetected	Moderate
Ketamine+Midazolam vs. Lidocaine	1	91	--	-1.50 (-2.05, -0.95)	Serious	Not serious	Not serious	Serious	Undetected	Low

CoE: certainty of evidence

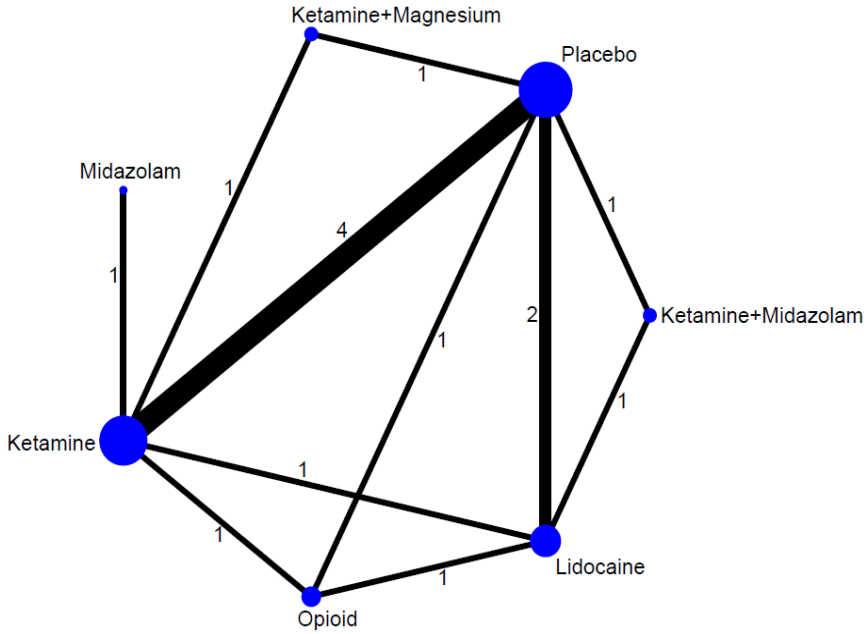
Table 3.17. Results of network meta-analysis with certainty of evidence for pain reduction at long-term follow-up time

Ketamine							
-2.70 (-3.33,-2.07)	Gabapentin						
0.01 (-0.97,0.99)	2.71 (1.54,3.88)	Ketamine+Midazolam					
0.10 (-2.98,3.18)	2.80 (-0.34,5.94)	0.09 (-3.14,3.32)	Ketamine+Methadone				
-1.49 (-2.45,-0.53)	1.21 (0.06,2.36)	-1.50 (-2.05,-0.95)	-1.59 (-4.82,1.64)	Lidocaine			
0.50 (-2.33,3.33)	3.20 (0.30,6.10)	0.49 (-2.51,3.49)	0.40 (-2.00,2.80)	1.99 (-1.00,4.98)	Methadone		
1.13 (-1.08,3.34)	3.83 (1.53,6.13)	1.12 (-1.30,3.54)	1.03 (-2.76,4.82)	2.62 (0.21,5.03)	0.63 (-2.96,4.22)	Midazolam	
0.28 (-3.07,3.63)	2.98 (-0.43,6.39)	0.27 (-3.22,3.76)	0.18 (-4.37,4.73)	1.77 (-1.72,5.25)	-0.22 (-4.61,4.17)	-0.85 (-4.86,3.16)	NSAIDs
-1.09 (-1.86,-0.32)	1.61 (0.61,2.61)	-1.10 (-1.71,-0.49)	-1.19 (-4.36,1.99)	0.40 (-0.17,0.97)	-1.59 (-4.52,1.35)	-2.22 (-4.56,0.12)	-1.37 (-4.81,2.07)	Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.7. Network map of physical function



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.18. Indirect estimates of effect for the network of physical function at short follow-up and P value for pairwise inconsistency

Comparison	Indirect Mean (95% CI)	IF (Se)	Inconsistency P value
Ketamine+Midazolam vs. Lidocaine	29.67 (2.69, 56.64)	-30.27 (14.42)	0.036 *
Ketamine+Midazolam vs. Placebo	-20.17 (-46.85, 6.51)	30.27 (14.42)	0.036 *
Ketamine vs. Ketamine+Magnesium	15.61 (-20.59, 51.81)	-15.61 (20.23)	0.44
Ketamine vs. Lidocaine	-7.10 (-21.51, 7.31)	15.99 (10.05)	0.111
Ketamine vs. Opioid	-11.44 (-48.93, 26.05)	12.23 (21.38)	0.567
Ketamine vs. Placebo	33.64 (6.36, 60.91)	-30.27 (14.42)	0.036 *
Ketamine+Magnesium vs. Placebo	15.61 (-20.65, 51.87)	-15.61 (20.23)	0.441
Lidocaine vs. Opioid	22.32 (-3.66, 48.30)	-30.27 (14.42)	0.036 *
Lidocaine vs. Placebo	-7.81 (-47.53, 31.91)	12.23 (21.38)	0.567
Opioid vs. Placebo	13.73 (-20.13, 47.59)	-9.17 (20.05)	0.647

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.814

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error, * Statistically significant inconsistency

Table 3.19. Results of direct pairwise comparisons with number of trials and certainty of evidence for physical function

Comparison	# RCTs	# participants	I^2	Direct Mean (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs. Midazolam	1	24	--	2.35 (-13.96, 18.66)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Ketamine+Magnesium	1	40	--	0.00 (-6.06, 6.06)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs. Placebo	4	169	85	15.20 (1.28, 29.12)	Serious	Not serious	Very serious	Very serious	Undetected	Very Low
Ketamine vs. Lidocaine	1	36	--	8.74 (-0.35, 17.83)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs. Opioid	1	36	--	0.79 (-8.66, 10.24)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs. Placebo	1	40	--	0.00 (-5.94, 5.94)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine+Midazolam vs. Placebo	1	90	--	10.10 (4.80, 15.40)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs. Placebo	2	125	85	4.29 (-9.47, 18.04)	Very serious	Not serious	Very serious	Very serious	Undetected	Very Low
Opioid vs. Placebo	1	36	--	4.56 (-5.33, 14.45)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Midazolam vs. Lidocaine	1	91	--	-0.60 (-5.38, 4.18)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Lidocaine vs. Opioid	1	36	--	-7.95 (-16.82, 0.92)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence

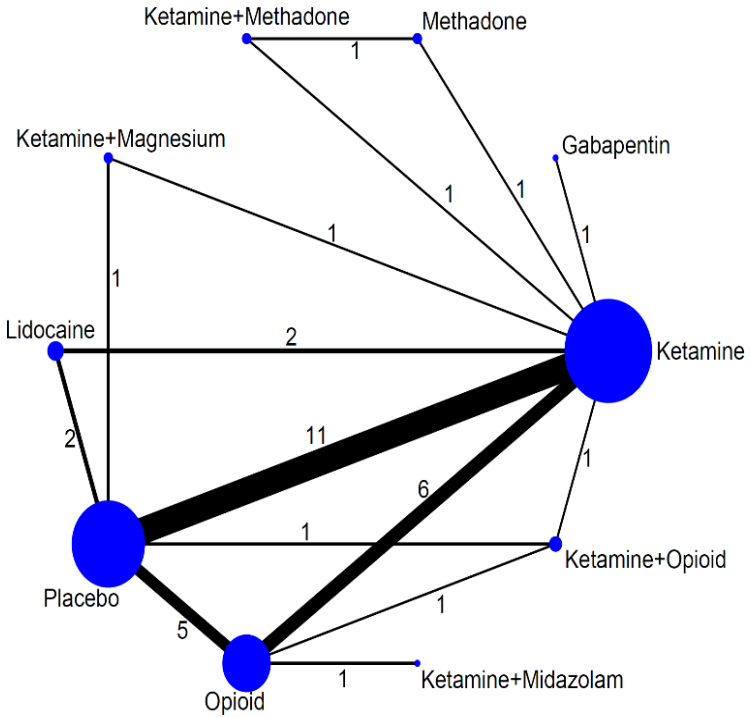
Table 3.20. Results of network meta-analysis with certainty of evidence for physical function

Ketamine					
-1.14 (-17.36,15.08)	Ketamine+Midazolam				
2.63 (-11.58,16.85)	3.77 (-16.11,23.65)	Ketamine+Magnesium			
1.82 (-10.67,14.31)	2.96 (-11.26,17.18)	-0.81 (-18.10,16.47)	Lidocaine		
2.35 (-19.36,24.06)	3.49 (-23.61,30.59)	-0.28 (-26.23,25.67)	0.53 (-24.52,25.58)	Midazolam	
-1.71 (-17.07,13.65)	-0.57 (-20.02,18.87)	-4.34 (-24.13,15.44)	-3.53 (-19.12,12.07)	-4.06 (-30.65,22.53)	Opioid
5.24 (-3.72,14.19)	6.38 (-7.93,20.68)	2.60 (-11.59,16.80)	3.42 (-7.45,14.29)	2.89 (-20.60,26.38)	6.95 (-8.01,21.91) Placebo

Results are mean differences (95% CIs) from the network meta-analysis. For each comparison (column vs. row), mean < 0 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.8. Network map of Gastrointestinal adverse events



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.21. Indirect estimates of effect for the network of incidence of Gastrointestinal adverse events and P value for pairwise inconsistency

Comparison	Indirect RR (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs Placebo	0.19 (0.00, 103.54)	3.07 (3.22)	0.341
Ketamine vs Ketamine+Magnesium	1.83 (0.03, 132.37)	-0.60 (2.31)	0.794
Ketamine vs Ketamine+Opioid	0.82 (0.07, 9.10)	-1.42 (1.81)	0.434
Ketamine vs Lidocaine	1.18 (0.04, 39.20)	0.19 (1.83)	0.917
Ketamine vs Opioid	0.32 (0.02, 5.51)	0.53 (1.50)	0.722
Ketamine+Magnesium vs Placebo	5.49 (0.21, 143.43)	-0.60 (2.31)	0.794
Ketamine+Opioid vs. Placebo	8.44 (0.28, 253.20)	0.58 (2.96)	0.846
Ketamine+Opioid vs. Opioid	5.38 (0.25, 115.00)	-1.37 (1.66)	0.408
Lidocaine vs. Placebo	2.49 (0.20, 30.99)	0.19 (1.83)	0.917
Opioid vs. Placebo	7.97 (1.27, 50.02)	-0.1. (1.33)	0.937

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.923

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.22. Results of direct pairwise comparisons with number of trials and certainty of evidence for incidence of Gastrointestinal adverse event

Comparison	# RCTs	# participants	I^2	Direct RR (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Gabapentin vs Ketamine	1	40	--	0.20 (0.01, 3.92)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Methadone	1	24	--	0.30 (0.04, 2.27)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Ketamine+Methadone	1	24	--	0.39 (0.05, 3.27)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Ketamine+Magnesium	1	40	--	1.00 (0.23, 4.37)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs Lidocaine	2	44	0	1.47 (0.49, 4.42)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs placebo	11	390	0	3.94 (2.16, 7.18)	Serious	Not serious	Not serious	Very serious	Not serious*	Very Low
Ketamine vs Opioid	6	148	0	0.50 (0.27, 0.93)	Serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs Ketamine+Opioid	1	40	--	0.14 (0.02, 1.06)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Methadone vs Methadone	1	26	--	0.75 (0.21, 2.71)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs Placebo	1	40	--	3.00 (0.34, 26.45)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Lidocaine vs. Placebo	2	44	0	3.00 (0.52, 17.20)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Opioid vs. Placebo	5	116	0	8.24 (2.31, 29.43)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine+Opioid vs. Placebo	1	40	--	15.00 (0.91, 246.20)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Midazolam vs. Opioid	1	52	--	0.40 (0.09, 1.88)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Opioid vs. Opioid	1	40	--	1.40 (0.53, 3.68)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Gabapentin vs Ketamine	1	40	--	0.20 (0.01, 3.92)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence * Harbord test p value: 0.515

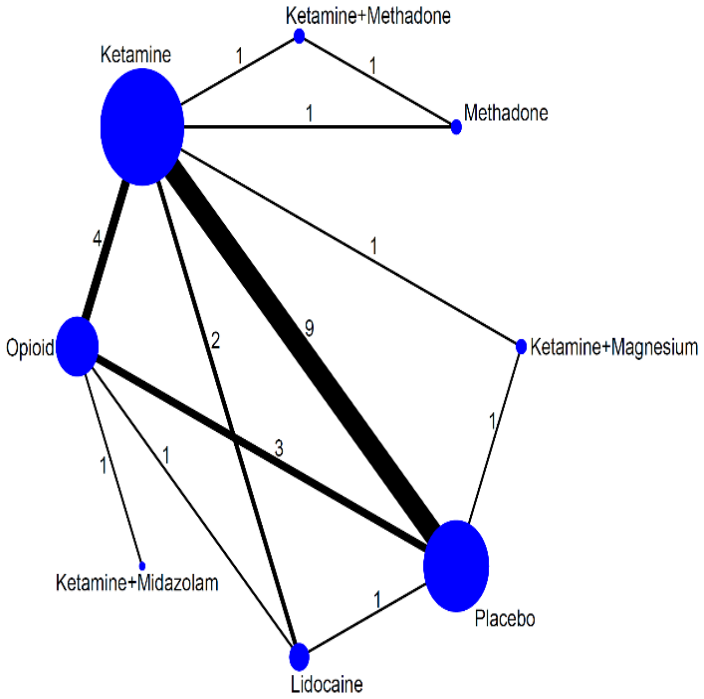
Table 3.23. Results of network meta-analysis with certainty of evidence for incidence of Gastrointestinal adverse events

Ketamine									
5.00 (0.26,98.00)	Gabapentin								
1.33 (0.26,6.84)	0.27 (0.01,7.94)	Ketamine+Midazolam							
1.07 (0.26,4.30)	0.21 (0.01,5.70)	0.80 (0.09,6.85)	Ketamine+Magnesium						
0.39 (0.05,3.27)	0.08 (0.00,3.03)	0.30 (0.02,4.30)	0.37 (0.03,4.66)	Ketamine+Methadone					
0.34 (0.13,0.89)	0.07 (0.00,1.55)	0.26 (0.04,1.51)	0.32 (0.06,1.72)	0.87 (0.09,8.83)	Ketamine+Opioid				
1.42 (0.51,3.91)	0.28 (0.01,6.57)	1.06 (0.16,7.28)	1.33 (0.24,7.40)	3.59 (0.34,37.58)	4.14 (1.03,16.60)	Lidocaine			
0.30 (0.04,2.27)	0.06 (0.00,2.18)	0.22 (0.02,3.03)	0.28 (0.02,3.28)	0.75 (0.21,2.71)	0.87 (0.09,8.21)	0.21 (0.02,2.04)	Methadone		
0.53 (0.31,0.91)	0.11 (0.01,2.19)	0.40 (0.09,1.88)	0.50 (0.11,2.21)	1.35 (0.15,11.99)	1.56 (0.66,3.69)	0.38 (0.12,1.18)	1.80 (0.22,14.83)	Opioid	
3.97 (2.18,7.22)	0.79 (0.04,16.51)	2.98 (0.53,16.61)	3.72 (0.86,16.06)	10.07 (1.12,90.80)	11.61 (3.95,34.11)	2.80 (0.90,8.71)	13.43 (1.60,112.42)	7.45 (3.53,15.73)	Placebo

Results are risk ratio (95% CIs) from the network meta-analysis. For each comparison (column vs. row), RR < 1 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.9. Network map of dizziness adverse events



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.24. Indirect estimates of effect for the network of incidence of dizziness adverse event and P value for pairwise inconsistency

Comparison	Indirect RR (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs Placebo	0.21 (0.00, 112.88)	2.87 (3.19)	0.368
Ketamine vs Ketamine+Magnesium	3.18 (0.00, 5632.16)	-2.77 (4.59)	0.547
Ketamine vs. Lidocaine	0.65 (0.01, 52.29)	0.92 (2.43)	0.705
Ketamine vs Opioid	0.78 (0.01, 48.56)	0.79 (2.19)	0.72
Ketamine+Magnesium vs Placebo	79.47 (0.04, 140803.98)	-2.77 (4.59)	0.547
Lidocaine vs Placebo	4.68 (0.35, 62.31)	-1.54 (2.15)	0.473
Lidocaine vs Opioid	0.37 (0.02, 5.81)	2.31 (2.05)	0.262
Opioid vs Placebo	0.53 (0.04, 7.41)	2.34 (1.80)	0.194

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.451

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.25. Results of direct pairwise comparisons with number of trials and certainty of evidence for incidence of dizziness adverse event

Comparison	# RCTs	# participants	I^2	Direct RR (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs Opioid	4	92	0	1.59 (0.56, 4.52)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs. Lidocaine	2	56	0	1.60 (0.08, 31.56)	Very serious	Not serious	Serious	Serious	Undetected	Very Low
Ketamine vs Placebo	9	286	0	4.24 (1.40, 12.80)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs Ketamine+Magnesium	1	40	--	0.20 (0.01, 3.92)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs Methadone	1	24	--	2.36 (0.25, 22.70)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Ketamine+Methadone	1	24	--	5.83 (0.31, 109.99)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Midazolam vs. Opioid	1	52	--	1.06 (0.72, 1.55)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Lidocaine vs Opioid	1	36	--	3.00 (0.34, 26.19)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Opioid vs Placebo	3	56	0	10.11 (1.38, 73.84)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Lidocaine vs Placebo	1	20	--	1.00 (0.07, 13.87)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs Placebo	1	40	--	5.00 (0.26, 98.00)	Very serious	Not serious	Not serious	Not serious	Undetected	Very Low
Ketamine+Methadone vs Methadone	1	26	--	0.33 (0.01, 7.50)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence

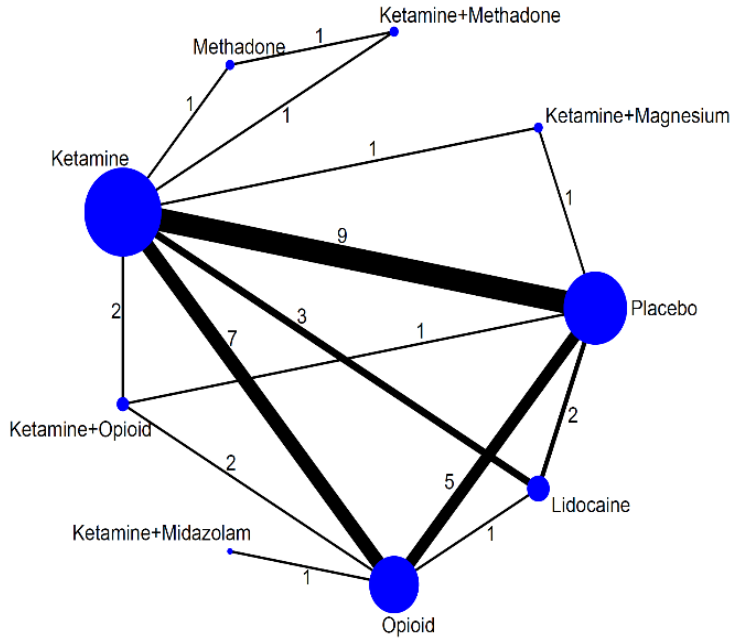
Table 3.26. Results of network meta-analysis with certainty of evidence for incidence of dizziness

Ketamine						
1.51 (0.15,15.61)	Ketamine+Midazolam					
0.38 (0.02,6.75)	0.25 (0.01,9.94)	Ketamine+Magnesium				
5.83 (0.17,198.06)	3.85 (0.06,264.00)	15.25 (0.16,1437.98)	Ketamine+Methadone			
1.40 (0.23,8.51)	0.92 (0.06,15.18)	3.65 (0.13,105.44)	0.24 (0.00,12.58)	Lidocaine		
1.94 (0.13,29.00)	1.28 (0.04,45.63)	5.08 (0.10,262.18)	0.33 (0.01,13.13)	1.39 (0.05,35.91)	Methadone	
1.60 (0.47,5.46)	1.06 (0.15,7.71)	4.19 (0.19,92.00)	0.27 (0.01,11.47)	1.15 (0.16,8.26)	0.82 (0.04,16.03)	Opioid
3.66 (1.25,10.74)	2.42 (0.20,29.11)	9.56 (0.54,168.85)	0.63 (0.02,25.00)	2.62 (0.35,19.43)	1.88 (0.10,34.50)	2.28 (0.51,10.23) Placebo

Results are risk ratio (95% CIs) from the network meta-analysis. For each comparison (column vs. row), RR < 1 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.10. Network map of fatigue, somnolence, and sedation



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.27. Indirect estimates of effect for the network of incidence of fatigue, somnolence, and sedation and P value for pairwise inconsistency

Comparison	Indirect RR (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs Placebo	1.64 (0.40, 6.82)	0.57 (0.7)	0.413
Ketamine vs Ketamine+Magnesium	7.55 (0.52, 108.82)	-1.73 (1.47)	0.239
Ketamine vs Ketamine+Opioid	0.61 (0.27, 1.38)	0.25 (0.47)	0.591
Ketamine vs Lidocaine	2.14 (0.75, 6.12)	-0.46 (0.54)	0.392
Ketamine vs Opioid	0.43 (0.12, 1.51)	0.64 (0.66)	0.329
Ketamine+Magnesium vs Placebo	5.67 (0.47, 67.73)	-1.73 (1.47)	0.239
Ketamine+Opioid vs Placebo	2.55 (0.62, 10.45)	0.62 (1.06)	0.556
Ketamine+Opioid vs Opioid	0.92 (0.37, 2.30)	0.14 (0.48)	0.776
Lidocaine vs Placebo	1.57 (0.61, 4.08)	0.45 (0.63)	0.477
Lidocaine vs Opioid	0.65 (0.43, 0.96)	-0.5 (0.43)	0.243
Opioid vs Placebo	4.49 (1.97, 10.23)	-0.31 (0.51)	0.536

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.877

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

Table 3.28. Results of direct pairwise comparisons with number of trials and certainty of evidence for incidence of fatigue, somnolence, and sedation

Comparison	# RCTs	# participants	I^2	Direct RR (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Ketamine vs Ketamine+Magnesium	1	40	--	1.33 (0.34, 5.21)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine vs Placebo	9	237	0	2.98 (1.90, 4.68)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs Lidocaine	3	80	0	1.34 (0.99, 1.80)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs Opioid	7	173	0	0.83 (0.58, 1.19)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs. Ketamine+Opioid	1	40	--	0.79 (0.60, 1.04)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Methadone	1	24	--	0.20 (0.06, 0.70)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs Ketamine+Methadone	1	24	--	0.39 (0.10, 1.57)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs Placebo	1	40	--	1.00 (0.23, 4.37)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Lidocaine vs Placebo	2	36	0	2.56 (1.16, 5.65)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Opioid vs Placebo	5	120	0	3.96 (1.98, 7.91)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine+Opioid vs Placebo	1	40	--	4.75 (1.97, 11.48)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs Opioid	1	36	--	0.42 (0.18, 0.94)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine+Opioid vs Opioid	1	40	--	1.06 (0.88, 1.26)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Midazolam vs Opioid	1	52	--	1.29 (0.83, 1.99)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Methadone vs Methadone	1	26	--	0.50 (0.27, 0.92)	Serious	Not serious	Not serious	Serious	Undetected	Low

CoE: certainty of evidence

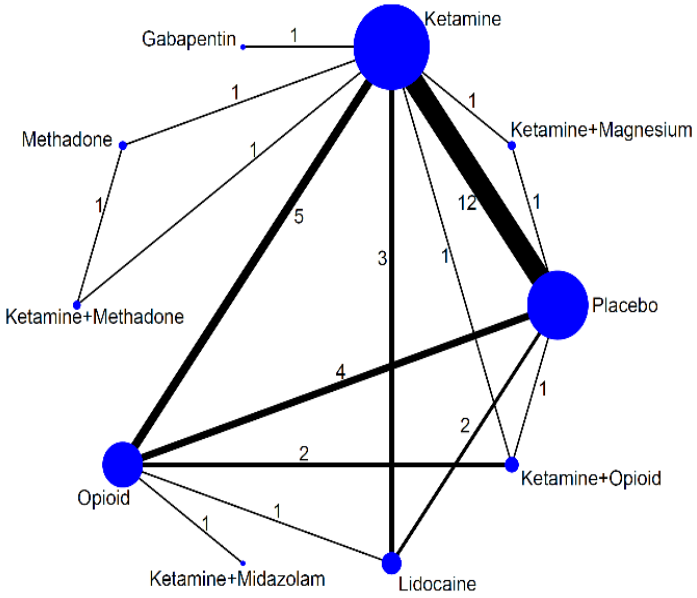
Table 3.29. Results of network meta-analysis with certainty of evidence for incidence of fatigue, somnolence, and sedation

Ketamine							
0.62 (0.38,1.02)	Ketamine+Midazolam						
1.84 (0.52,6.44)	2.96 (0.77,11.36)	Ketamine+Magnesium					
0.39 (0.10,1.57)	0.64 (0.15,2.76)	0.21 (0.03,1.39)	Ketamine+Methadone				
0.76 (0.60,0.96)	1.23 (0.77,1.96)	0.41 (0.12,1.48)	1.93 (0.47,7.85)	Ketamine+Opioid			
1.38 (1.03,1.84)	2.22 (1.26,3.90)	0.75 (0.21,2.71)	3.49 (0.85,14.37)	1.81 (1.26,2.60)	Lidocaine		
0.20 (0.06,0.70)	0.32 (0.08,1.23)	0.11 (0.02,0.64)	0.50 (0.27,0.92)	0.26 (0.07,0.94)	0.14 (0.04,0.52)	Methadone	
0.80 (0.63,1.00)	1.29 (0.83,1.99)	0.43 (0.12,1.55)	2.02 (0.50,8.23)	1.05 (0.88,1.24)	0.58 (0.41,0.83)	4.05 (1.12,14.61)	Opioid
2.89 (1.84,4.53)	4.66 (2.44,8.89)	1.57 (0.44,5.59)	7.33 (1.71,31.42)	3.80 (2.36,6.12)	2.10 (1.24,3.55)	14.66 (3.84,56.05)	3.62 (2.26,5.82)	Placebo

Results are risk ratio (95% CIs) from the network meta-analysis. For each comparison (column vs. row), RR < 1 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.11. Network map of dissociative symptoms



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.30. Indirect estimates of effect for the network of incidence of dissociative symptoms and P value for pairwise inconsistency

Comparison	Indirect RR (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs Placebo	81.97 (3.03, 2220.89)	-2.99 (1.66)	0.072 *
Ketamine vs Ketamine+Magnesium	1.18 (0.00, 552.68)	0.35 (3.24)	0.915
Ketamine vs Ketamine+Opioid	1.11 (0.13, 9.32)	-0.1 (1.62)	0.949
Ketamine vs Lidocaine	0.19 (0.01, 3.42)	2.55 (1.44)	0.076 *
Ketamine vs Opioid	0.93 (0.07, 12.10)	0.99 (1.32)	0.457
Ketamine+Magnesium vs Placebo	2.12 (0.03, 173.37)	0.35 (3.24)	0.915
Ketamine+Opioid vs Placebo	6.56 (0.71, 60.59)	-1.35 (2.06)	0.512
Ketamine+Opioid vs Opioid	14.81 (0.29, 769.66)	-2.12 (2.09)	0.311
Lidocaine vs Placebo	0.32 (0.04, 2.44)	3.24 (1.72)	0.59
Lidocaine vs Opioid	0.96 (0.26, 3.57)	0.15 (1.72)	0.931
Opioid vs Placebo	0.64 (0.16, 2.66)	2.02 (1.12)	0.071 *

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.337

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error

* Statistically significant loop-specific incoherence

Table 3.31. Results of direct pairwise comparisons with number of trials and certainty of evidence for incidence of dissociative symptoms

Comparison	# RCTs	# participants	I^2	Direct RR (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Gabapentin vs Ketamine	1	40	--	35.00 (2.25, 544.92)	Serious	Not serious	Not serious	Serious	Undetected	Low
Ketamine vs Methadone	1	24	--	3.50 (0.16, 78.19)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Ketamine+Methadone	1	24	--	3.50 (0.16, 78.19)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Opioid	5	132	0	2.58 (1.12, 5.91)	Serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs Lidocaine	3	80	0	2.76 (1.20, 6.35)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs Ketamine+Opioid	1	40	--	1.00 (0.07, 14.90)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Placebo	12	432	0	4.08 (2.40, 6.96)	Serious	Not serious	Not serious	Very serious	Not serious*	Very Low
Ketamine vs Ketamine+Magnesium	1	40	--	2.00 (0.20, 20.33)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine+Midazolam vs Opioid	1	52	--	2.08 (1.37, 3.18)	Serious	Not serious	Not serious	Serious	Undetected	Low
Lidocaine vs Opioid	1	36	--	0.33 (0.01, 7.68)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Opioid vs Opioid	2	75	0	1.81 (0.17, 19.44)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Opioid vs Placebo	4	96	0	6.82 (0.88, 52.75)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Lidocaine vs Placebo	2	44	0	6.78 (0.89, 51.49)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine+Opioid vs Placebo	1	40	--	3.00 (0.13, 69.52)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine+Magnesium vs Placebo	1	40	--	3.00 (0.13, 69.52)	Very serious	Not serious	Not serious	Not serious	Undetected	Low

CoE: certainty of evidence

* Harbord test p value: 0.812

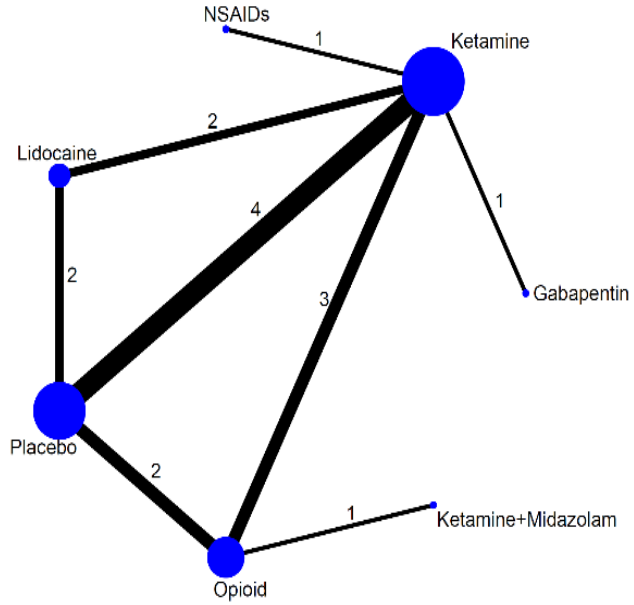
Table 3.32. Results of network meta-analysis with certainty of evidence for incidence of dissociative symptoms

Ketamine								
0.03 (0.00,0.50)	Gabapentin							
1.13 (0.33,3.81)	39.38 (1.75,885.14)	Ketamine+Midazolam						
1.62 (0.21,12.29)	56.61 (1.69,1892.21)	1.44 (0.14,15.26)	Ketamine+Magnesium					
3.50 (0.14,86.89)	122.49 (1.66,9058.31)	3.11 (0.10,96.54)	2.16 (0.05,96.58)	Ketamine+Methadone				
1.06 (0.22,5.00)	37.06 (1.43,962.77)	0.94 (0.17,5.23)	0.65 (0.05,8.38)	0.30 (0.01,10.71)	Ketamine+Opioid			
2.39 (1.00,5.68)	83.54 (4.19,1664.93)	2.12 (0.48,9.36)	1.48 (0.16,13.36)	0.68 (0.02,18.99)	2.25 (0.38,13.25)	Lidocaine		
3.50 (0.14,86.89)	122.49 (1.66,9058.31)	3.11 (0.10,96.54)	2.16 (0.05,96.58)	1.00 (0.02,51.16)	3.31 (0.09,117.03)	1.47 (0.05,40.83)	Methadone	
2.34 (1.05,5.22)	82.04 (4.19,1604.99)	2.08 (0.83,5.22)	1.45 (0.16,12.78)	0.67 (0.02,18.34)	2.21 (0.52,9.41)	0.98 (0.31,3.15)	0.67 (0.02,18.34)	Opioid
4.22 (2.20,8.10)	147.76 (7.83,2787.52)	3.75 (0.97,14.46)	2.61 (0.32,21.21)	1.21 (0.05,31.97)	3.99 (0.77,20.72)	1.77 (0.62,5.07)	1.21 (0.05,31.97)	1.80 (0.67,4.83)	Placebo

Results are risk ratio (95% CIs) from the network meta-analysis. For each comparison (column vs. row), RR < 1 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

Figure 3.12. Network map of visual impairment



The size of the node (circle) corresponds to the number of patients randomized to that intervention.

The thickness of the lines corresponds to the number of studies for each comparison.

Table 3.33. Indirect estimates of effect for the network of incidence of visual impairment and P value for pairwise inconsistency

Comparison	Indirect RR (95% CI)	IF (Se)	Inconsistency P value
Ketamine vs Lidocaine	1.94 (0.01, 378.85)	1.12 (2.62)	0.669
Ketamine vs Opioid	10.03 (0.06, 1678.35)	-1.12 (2.62)	0.669
Lidocaine vs Placebo	0.77 (0.01, 48.95)	1.12 (2.62)	0.669
Opioid vs Placebo	7.57 (0.08, 682.33)	-1.12 (2.62)	0.669

All the evidence comes from trials which directly compare them. Significant inconsistency P value means estimates from direct and indirect comparison are statistically different. P value for global test of inconsistency = 0.669

Statistical tests of inconsistency have low power and thus typically is p value < 0.1 is considered as important inconsistency.

IF: inconsistency factor; Se: standard error,

Table 3.34. Results of direct pairwise comparisons with number of trials and certainty of evidence for visual impairment

Comparison	# RCTs	# participants	I^2	Direct RR (95% CI)	Precision	Directness	Consistency	Overall RoB	Publication bias	COE
Gabapentin vs Ketamine	1	40	--	3.00 (0.13, 69.52)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low
Ketamine vs Opioid	3	56	0	3.07 (0.55, 17.17)	Very serious	Not serious	Serious	Very serious	Undetected	Very Low
Ketamine vs Placebo	4	100	0	11.66 (2.92, 46.65)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs Lidocaine	2	44	0	8.18 (1.66, 40.28)	Serious	Not serious	Not serious	Very serious	Undetected	Very Low
Ketamine vs NSAIDs	1	40	--	1.00 (0.07, 14.90)	Very serious	Not serious	Not serious	Not serious	Undetected	Low
Ketamine+Midazolam vs Opioid	1	52	--	3.20 (1.38, 7.44)	Serious	Not serious	Not serious	Serious	Undetected	Low
Opioid vs Placebo	2	56	0	3.00 (0.34, 26.19)	Very serious	Not serious	Not serious	Very serious	Undetected	Very Low
Lidocaine vs Placebo	2	44	--	3.00 (0.13, 67.06)	Very serious	Not serious	Not serious	Serious	Undetected	Very Low

CoE: certainty of evidence

Table 3.35. Results of network meta-analysis with certainty of evidence for incidence of visual impairment

Ketamine						
0.33 (0.01,7.72)	Gabapentin					
1.06 (0.25,4.52)	3.17 (0.10,101.08)	Ketamine+Midazolam				
5.89 (1.48,23.39)	17.66 (0.57,546.56)	5.57 (0.75,41.19)	Lidocaine			
1.00 (0.07,14.90)	3.00 (0.05,189.26)	0.95 (0.04,20.36)	0.17 (0.01,3.53)	NSAIDs		
3.38 (1.03,11.03)	10.14 (0.35,291.37)	3.20 (1.38,7.44)	0.57 (0.09,3.52)	3.38 (0.18,64.53)	Opioid	
10.21 (2.86,36.42)	30.62 (1.03,908.88)	9.67 (1.59,58.67)	1.73 (0.27,11.00)	10.21 (0.52,202.17)	3.02 (0.61,14.86)	Placebo

Results are risk ratio (95% CIs) from the network meta-analysis. For each comparison (column vs. row), RR < 1 indicates the intervention in the column is superior to the comparator in the row.

High certainty of evidence	Moderate certainty of evidence	Low certainty of evidence	Very Low certainty of evidence

References

1. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl. 1986;3:S1-226.
2. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health. 2011;11(1):770.
3. Rice AS, Smith BH, Blyth FM. Pain and the global burden of disease. Pain. 2016;157(4):791-6.
4. Brain K, Burrows TL, Bruggink L, Malfliet A, Hayes C, Hodson FJ, et al. Diet and chronic non-cancer pain: The state of the art and future directions. Journal of clinical medicine. 2021;10(21):5203.
5. Reitsma ML, Tranmer JE, Buchanan DM, Vandenkerkhof EG. The prevalence of chronic pain and pain-related interference in the Canadian population from 1994 to 2008. Chronic Dis Inj Can. 2011;31(4):157-64.
6. Rikard SM, Strahan AE, Schmit KM, Guy GP, Jr. Chronic Pain Among Adults - United States, 2019-2021. MMWR Morb Mortal Wkly Rep. 2023;72(15):379-85.
7. Hadi MA, McHugh GA, Closs SJ. Impact of chronic pain on patients' quality of life: a comparative mixed-methods study. Journal of patient experience. 2019;6(2):133-41.
8. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. Journal of pain research. 2016:457-67.
9. Hurwitz EL, Randhawa K, Yu H, Côté P, Haldeman S. The Global Spine Care Initiative: a summary of the global burden of low back and neck pain studies. European Spine Journal. 2018;27(6):796-801.
10. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397(10289):2098-110.
11. Kendroud S, Fitzgerald LA, Murray IV, Hanna A. Physiology, Nociceptive Pathways. StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2024, StatPearls Publishing LLC.; 2024.
12. Murnion BP. Neuropathic pain: current definition and review of drug treatment. Aust Prescr. 2018;41(3):60-3.
13. Volcheck MM, Graham SM, Fleming KC, Mohabbat AB, Luedtke CA. Central sensitization, chronic pain, and other symptoms: Better understanding, better management. Cleve Clin J Med. 2023;90(4):245-54.
14. Campbell F HM, Choiniere M, El-Gabalawy H, Laliberte J, Sangster M, et al. Canadian Pain Task Force Report: October 2020. [cited 2024 23 Jun]. Available from:

https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2020.html#message.
15. Hogan ME, Taddio A, Katz J, Shah V, Krahn M. Incremental health care costs for chronic pain in Ontario, Canada: a population-based matched cohort study of adolescents and adults using administrative data. Pain. 2016;157(8):1626-33.
16. Park HJ, Moon DE. Pharmacologic management of chronic pain. Korean J Pain. 2010;23(2):99-108.
17. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.
18. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Cmaj. 2017;189(18):E659-e66.
19. Ferreira GE, Abdel-Shaheed C, Underwood M, Finnerup NB, Day RO, McLachlan A, et al. Efficacy, safety, and tolerability of antidepressants for pain in adults: overview of systematic reviews. bmj. 2023;380.
20. Atkinson TJ, Fudin J. Nonsteroidal Antiinflammatory Drugs for Acute and Chronic Pain. Phys Med Rehabil Clin N Am. 2020;31(2):219-31.
21. Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). Best Pract Res Clin Rheumatol. 2015;29(1):6-19.
22. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. Lancet. 2011;377(9784):2226-35.
23. Iacobucci GJ, Visnjevac O, Pourafkari L, Nader ND. Ketamine: An Update on Cellular and Subcellular Mechanisms with Implications for Clinical Practice. Pain Physician. 2017;20(2):E285-e301.
24. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg. 2003;97(4):1108-16.
25. Hirota K, Lambert D. Ketamine: new uses for an old drug? : Oxford University Press; 2011. p. 123-6.
26. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol. 2014;77(2):357-67.
27. Anderson P. Ketamine for chronic pain on the rise. 2017.
28. Culp C, Kim HK, Abdi S. Ketamine Use for Cancer and Chronic Pain Management. Front Pharmacol. 2020;11:599721.
29. Ling H-Q, Chen Z-H, He L, Feng F, Weng C-G, Cheng S-J, et al. Comparative efficacy and safety of 11 drugs as therapies for adults with neuropathic pain after spinal cord injury: a Bayesian network analysis based on 20 randomized controlled trials. Frontiers in neurology. 2022;13:818522.
30. Chah N, Jones M, Milord S, Al-Eryani K, Enciso R. Efficacy of ketamine in the treatment of migraines and other unspecified primary headache disorders compared

to placebo and other interventions: a systematic review. Journal of dental anesthesia and pain medicine. 2021;21(5):413.
31. Chitneni A, Patil A, Dalal S, Ghorayeb JH, Pham YN, Grigoropoulos G. Use of Ketamine Infusions for Treatment of Complex Regional Pain Syndrome: A Systematic Review. Cureus. 2021;13(10):e18910.
32. Jørum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine--a double-blind, cross-over comparison with alfentanil and placebo. Pain. 2003;101(3):229-35.
33. Sörensen J, Bengtsson A, Bäckman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. Scand J Rheumatol. 1995;24(6):360-5.
34. Sörensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. J Rheumatol. 1997;24(8):1615-21.
35. Ayesh EE, Jensen TS, Svensson P. Effects of intra-articular ketamine on pain and somatosensory function in temporomandibular joint arthralgia patients. Pain. 2008;137(2):286-94.
36. Michelet D, Brasher C, Horlin AL, Bellon M, Julien-Marsollier F, Vacher T, et al. Ketamine for chronic non-cancer pain: A meta-analysis and trial sequential analysis of randomized controlled trials. Eur J Pain. 2018;22(4):632-46.
37. Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP. Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials. Anesthesia & Analgesia. 2019;129(1):241-54.
38. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. Current pain and headache reports. 2018;22:1-8.
39. Guimarães Pereira JE, Ferreira Gomes Pereira L, Mercante Linhares R, Darcy Alves Bersot C, Aslanidis T, Ashmawi HA. Efficacy and Safety of Ketamine in the Treatment of Neuropathic Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Pain Res. 2022;15:1011-37.
40. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.
41. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
42. Chandler J, Cumpston M, Li T, Page MJ, Welch V. Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley. 2019.

43. Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. Res Synth Methods. 2011;2(3):188-203.
44. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. The journal of pain. 2008;9(2):105-21.
45. Ward MM, Guthrie LC, Alba MI. Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness. Arthritis care & research. 2014;66(12):1783-9.
46. Metelli S, Chaimani A, editors. NMAstudio: a fully interactive web-application for producing and visualising network meta-analyses. SRSM Annual Meeting; 2021.
47. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
48. Jackson D, Riley R, White IR. Multivariate meta-analysis: potential and promise. Stat Med. 2011;30(20):2481-98.
49. Sadeghirad B, Foroutan F, Zoratti MJ, Busse JW, Brignardello-Petersen R, Guyatt G, et al. Theory and practice of Bayesian and frequentist frameworks for network meta-analysis. BMJ Evid Based Med. 2023;28(3):204-9.
50. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98-110.
51. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932-44.
52. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25(20):3443-57.
53. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.
54. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018;93:36-44.
55. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
56. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. Bmj. 2014;349:g5630.
57. Collazo E, Ramírez Urbano I, González-Ripoll C. Ensayo clínico sobre la eficacia de varios procedimientos terapéuticos en el alivio del dolor en pacientes con fibromialgia. Revista Internacional de Acupuntura. 2015;9(3):87-94.

58. Kvarnström A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand. 2004;48(4):498-506.
59. Kvarnström A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand. 2003;47(7):868-77.
60. Lemming D, Sörensen J, Graven-Nielsen T, Arendt-Nielsen L, Gerdle B. The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain. Clin J Pain. 2005;21(5):412-21.
61. Lemming D, Sörensen J, Graven-Nielsen T, Lauber R, Arendt-Nielsen L, Gerdle B. Managing chronic whiplash associated pain with a combination of low-dose opioid (remifentanil) and NMDA-antagonist (ketamine). Eur J Pain. 2007;11(7):719-32.
62. Lumanauw DD, Youn S, Horeczko T, Yadav K, Tanen DA. Subdissociative-dose Ketamine Is Effective for Treating Acute Exacerbations of Chronic Pain. Acad Emerg Med. 2019;26(9):1044-51.
63. Maher DP, Zhang Y, Ahmed S, Doshi T, Malarick C, Stabach K, et al. Chronic Opioid Therapy Modifies QST Changes After Ketamine Infusion in Chronic Pain Patients. J Pain. 2017;18(12):1468-75.
64. Carr DB, Goudas LC, Denman WT, Brookoff D, Staats PS, Brennen L, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. Pain. 2004;108(1-2):17-27.
65. Castrillon EE, Cairns BE, Ernberg M, Wang K, Sessle BJ, Arendt-Nielsen L, et al. Effect of peripheral NMDA receptor blockade with ketamine on chronic myofascial pain in temporomandibular disorder patients: a randomized, double-blinded, placebo-controlled trial. J Orofac Pain. 2008;22(2):122-30.
66. Dadabayev AR, Joshi SA, Reda MH, Lake T, Hausman MS, Domino E, et al. Low Dose Ketamine Infusion for Comorbid Posttraumatic Stress Disorder and Chronic Pain: A Randomized Double-Blind Clinical Trial. Chronic Stress (Thousand Oaks). 2020;4:2470547020981670.
67. Lauretti G, Matsumoto M, Mattos A, Lanchote V, Pereira N. The clinical and laboratorial evaluation of transdermal ketamine, fentanyl, Clonidine or their combination in chronic low back pain. Coluna/Columna. 2009;8:434-40.
68. Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. Clin Neuropharmacol. 1995;18(4):360-8.
69. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. Pain. 2002;97(3):275-81.
70. Muller A, Rempp C, Kopferschmitt J, Haeringer M-T, Brandt C, Meyer P, et al. Effets de la kétamine administrée par voie veineuse pendant trois jours sur les

douleurs de fibromyalgie: Étude en double-aveugle, « cross-over », versus placebo. Douleurs : Evaluation - Diagnostic - Traitement. 2005;6(3):151-9.
71. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. Br J Anaesth. 2013;110(6):1010-6.
72. Pickering G, Pereira B, Morel V, Corriger A, Giron F, Marcaillou F, et al. Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-blind, Crossover Trial. Anesthesiology. 2020;133(1):154-64.
73. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009;147(1-3):107-15.
74. Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous SM, Marinus J, Sarton EY, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009;145(3):304-11.
75. Vranken JH, Dijkgraaf MGW, Kruis MR, van Dasselaar NT, van der Vegt MH. Iontophoretic administration of S(+)-ketamine in patients with intractable central pain: A placebo-controlled trial. PAIN. 2005;118(1).
76. Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain. 2011;15(9):942-9.
77. Persson J, Hasselström J, Wiklund B, Heller A, Svensson JO, Gustafsson LL. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Acta Anaesthesiol Scand. 1998;42(7):750-8.
78. Amr YM. Epidural ketamine in post spinal cord injury-related chronic pain. Anesth Essays Res. 2011;5(1):83-6.
79. Jafarinia M, Afarideh M, Tafakhori A, Arbabi M, Ghajar A, Noorbala AA, et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: A double-blind, randomized, controlled trial. J Affect Disord. 2016;204:1-8.
80. Lauretti GR, Rodrigues AdM, Gomes JMA, Reis MPd. Epidural ketamine versus epidural clonidine as therapeutic for refractory neuropathic chronic pain. Revista Brasileira De Anestesiologia. 2002;52:34-40.
81. Rigo FK, Trevisan G, Godoy MC, Rossato MF, Dalmolin GD, Silva MA, et al. Management of Neuropathic Chronic Pain with Methadone Combined with Ketamine: A Randomized, Double Blind, Active-Controlled Clinical Trial. Pain Physician. 2017;20(3):207-15.
82. Kim YH, Lee PB, Oh TK. Is magnesium sulfate effective for pain in chronic postherpetic neuralgia patients comparing with ketamine infusion therapy? J Clin Anesth. 2015;27(4):296-300.

83. Amr YM. Effect of addition of epidural ketamine to steroid in lumbar radiculitis: one-year follow-up. Pain Physician. 2011;14(5):475-81.
84. Peter F, editor COMPARISON OF THE EFFICACY OF EPIDURAL KETAMINE VS ORAL GABAPENTIN FOR ANALGESIA IN CHRONIC PAIN DUE TO SPINAL INJURIES2023.
85. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain. 2001;91(1-2):177-87.
86. Bouwense SA, Buscher HC, van Goor H, Wilder-Smith OH. S-ketamine modulates hyperalgesia in patients with chronic pancreatitis pain. Reg Anesth Pain Med. 2011;36(3):303-7.
87. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain. 1994;58(3):347-54.
88. Rabben T, Skjelbred P, Oye I. Prolonged analgesic effect of ketamine, an N-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. J Pharmacol Exp Ther. 1999;289(2):1060-6.
89. Graven-Nielsen T, Kendall SA, Henriksson KG, Bengtsson M, Sörensen J, Johnson A, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain. 2000;85(3):483-91.
90. Haines DR, Gaines SP. N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. Pain. 1999;83(2):283-7.

91. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, Hurley RW, Viscusi ER, Narouze S, Davis FN, Ritchie EC, Lubenow TR, Hooten WM. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

92. Bell RF, Kalso EA. Ketamine for pain management. Pain Rep. 2018 Aug 9;3(5):e674.

Appendices

Appendix 1. Details of search strategy

April 20, 2022

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

---

1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (82468)
2 chronic pain/ (19551)
3 exp osteoarthritis/ (72012)
4 osteoarthrit*.mp. (103525)
5 osteo-arthritis.mp. (398)
6 degenerative arthrit*.mp. (1379)
7 exp Arthritis, Rheumatoid/ (121011)
8 exp Neuralgia/ (23217)
9 Diabetic Neuropathies/ (15733)
10 (neuropath* adj5 (pain* or diabet*)).mp. (48516)
11 neuralg*.mp. (31237)
12 fibromyalgia/ (9346)
13 fibromyalg*.mp. (13085)
14 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5825)
15 (complex regional pain syndromes or causalgia).mp. (2721)
16 Pain, Intractable/ (6321)
17 Phantom Limb/ (2011)
18 Hyperalgesia/ (13226)
19 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (21731)
20 or/1-19 (396992)
21 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (42786)
22 Radiculopathy/ or radiculopathy.mp. (10174)
23 musculoskeletal pain/ or headache/ (33956)
24 exp Arthralgia/ (14832)
25 exp Headache Disorders/ (38174)
26 headache*.mp. (104802)
27 Temporomandibular Joint Dysfunction Syndrome/ (4928)
28 ((TMJ or TMJD) and pain*).mp. (3099)

29 whiplash.mp. or exp whiplash injury/ (4122)
30 exp Cumulative Trauma Disorders/ (14737)
31 exp Peripheral Nervous System Diseases/dt (16604)
32 Pain Measurement/de (6914)
33 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (51148)
34 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (192417)
35 or/21-34 (383764)
36 (acute or emergency or preoperative or postoperative).ti,ab. (2201574)
37 35 not 36 (319135)
38 20 or 37 (623559)
Annotation: chronic pain concept
39 Ketamine.mp. or exp Ketamine/ (22328)
40 esketamine.mp. (449)
41 (ketamine or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine).tw. (20761)
42 or/39-41 (22489)
Annotation: ketamine
43 38 and 42 (1371)
44 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (1058546)
45 ((treatment or control) adj3 group*).ab. (684443)
46 (allocat* adj5 group*).ab. (30166)
47 ((clinical or control*) adj3 trial).ti,ab,kw. (336671)
48 or/44-47 (1659640)
49 43 and 48 (406)
50 exp animals/ not humans.sh. (4996406)
51 49 not 50 (372)

EMBASE (OVID)

Database: Embase <1974 to 2022 April 19>
Search Strategy:
---
1 (chronic adj4 pain*).mp. (133959)
2 chronic pain/ (69724)
3 exp osteoarthritis/ (145908)
4 osteoarthrit*.mp. (164013)
5 osteo-arthritis.mp. (456)
6 degenerative arthrit*.mp. (1663)
7 exp rheumatoid arthritis/ (220591)

8 exp neuralgia/ (116948)
9 diabetic neuropathy/ (26198)
10 (neuropath* adj5 (pain* or diabet*)).mp. (85494)
11 neuralg*.mp. (33618)
12 fibromyalgia/ (22867)
13 fibromyalg*.mp. (24838)
14 reflex sympathetic dystrophy.mp. (2387)
15 (complex regional pain syndromes or causalgia).mp. (1342)
16 intractable pain/ (5203)
17 phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (8171)
18 hyperalgesia/ (20458)
19 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (32212)
20 or/1-19 (687968)
21 exp backache/ (123745)
22 radiculopathy.mp. or exp radiculopathy/ (43898)
23 musculoskeletal pain/ (13271)
24 exp arthralgia/ (70322)
25 headache/ (244504)
26 headache*.mp. (314833)
27 temporomandibular joint disorder/ (15171)
28 ((TMJ or TMJD) and pain*).mp. (4206)
29 whiplash.mp. or whiplash injury/ (5186)
30 exp cumulative trauma disorder/ (23139)
31 or/21-30 (553204)
32 (acute or emergency or preoperative or postoperative).ti,ab. (3024074)
33 31 not 32 (459070)
34 20 or 33 (1058825)
35 Ketamine.mp. or exp Ketamine/ (52371)
36 esketamine.mp. (1084)
37 (ketamine or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine).tw. (29769)
38 or/35-37 (52867)
39 34 and 38 (4805)
40 randomized controlled trial/ (705694)
41 Controlled clinical study/ (465517)
42 random$.ti,ab. (1779890)
43 randomization/ (93736)
44 intermethod comparison/ (282199)
45 placebo.ti,ab. (339623)
46 (compare or compared or comparison).ti. (562566)
47 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2483089)
48 (open adj label).ti,ab. (96365)
49 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (255555)

50 double blind procedure/ (194240)
51 parallel group$1.ti,ab. (29227)
52 (crossover or cross over).ti,ab. (115826)
53 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (377736)
54 (assigned or allocated).ti,ab. (444876)
55 (controlled adj7 (study or design or trial)).ti,ab. (405366)
56 (volunteer or volunteers).ti,ab. (266893)
57 human experiment/ (572558)
58 trial.ti. (356483)
59 or/40-58 (5737088)
60 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8944)
61 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (306579)
62 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (19695)
63 (Systematic review not (trial or study)).ti. (207048)
64 (nonrandom$ not random$).ti,ab. (17727)
65 "Random field$".ti,ab. (2696)
66 (random cluster adj3 sampl$).ti,ab. (1432)
67 (review.ab. and review.pt.) not trial.ti. (985580)
68 "we searched".ab. and (review.ti. or review.pt.) (41477)
69 "update review".ab. (123)
70 (databases adj4 searched).ab. (50076)
71 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1146315)
72 Animal experiment/ not (human experiment/ or human/) (2405937)
73 or/60-72 (3941197)
74 59 not 73 (5082651)
75 39 and 74 (769)

Cochrane Library (Wiley)
Search Name:
Date Run: 20/04/2022 19:04:33
Comment:

ID	Search	Hits
#1	(chronic near/3 pain):ti,ab,kw (Word variations have been searched)	18860
#2	MeSH descriptor: [Chronic Pain] explode all trees	2983
#3	MeSH descriptor: [Osteoarthritis] explode all trees	8382
#4	osteoarthrit*	20642
#5	osteo-arthritis	189
#6	degenerative arthrit*	465
#7	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	6436

#8 MeSH descriptor: [Neuralgia] explode all trees 1848
#9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 2307
#10 neuropath* near/5 (pain* or diabet*) 8033
#11 neuralg* 3284
#12 MeSH descriptor: [Fibromyalgia] explode all trees 1546
#13 fibromyalg* 3478
#14 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 321
#15 complex regional pain syndromes or causalgia 420
#16 MeSH descriptor: [Pain, Intractable] explode all trees 275
#17 MeSH descriptor: [Phantom Limb] explode all trees 150
#18 MeSH descriptor: [Hyperalgesia] explode all trees 631
#19 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) near/3 pain) 3886
#20 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 58898
#21 MeSH descriptor: [Back Pain] explode all trees 5573
#22 MeSH descriptor: [Radiculopathy] explode all trees 514
#23 MeSH descriptor: [Musculoskeletal Pain] explode all trees 1172
#24 MeSH descriptor: [Arthralgia] explode all trees 2062
#25 MeSH descriptor: [Headache Disorders] explode all trees 3711
#26 MeSH descriptor: [Headache] explode all trees 2543
#27 headache* 37202
#28 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 348
#29 ((TMJ or TMJD) and pain*) 514
#30 MeSH descriptor: [Whiplash Injuries] explode all trees 224
#31 whiplash 549
#32 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 955
#33 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* 20213

#34 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 52668
#35 radiculopathy 1580
#36 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 96832
#37 acute or emergency or preoperative or postoperative 315002
#38 #36 not #37 74840
#39 #20 or #38 110553
#40 MeSH descriptor: [Ketamine] explode all trees 2422
#41 ketamine or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine 6115
#42 #40 or #41 6115

#43 #39 and #42 in Trials 616

PsycInfo (OVID)

Database: APA PsycInfo <1806 to April Week 2 2022>
Search Strategy:
---
1 (chronic adj4 pain*).mp. (25478)
2 chronic pain/ (14929)
3 exp Arthritis/ (4527)
4 osteoarthrit*.mp. (2404)
5 osteo-arthritis.mp. (8)
6 degenerative arthrit*.mp. (15)
7 exp Neuralgia/ (997)
8 neuropathy/ (3638)
9 (neuropath* adj5 (pain* or diabet*)).mp. (7692)
10 neuralg*.mp. (3637)
11 fibromyalgia/ (2216)
12 fibromyalg*.mp. (3757)
13 complex regional pain syndromes.mp. (334)
14 "complex regional pain syndrome (type i)"/ (183)
15 (complex regional pain syndromes or causalgia).mp. (425)
16 somatosensory disorders/ (1583)
17 hyperalgesi*.mp. (5735)
18 somatoform pain disorder/ or somatoform disorders/ or conversion disorder/ (9754)
19 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (3726)
20 or/1-19 (54773)
21 back pain.mp. or exp Back Pain/ (6935)
22 radiculopathy.mp. (359)
23 musculoskeletal pain.mp. (2053)
24 Arthralgia.mp. (353)
25 headache.mp. or exp HEADACHE/ (21618)
26 ((TMJ or TMJD) and pain*).mp. (160)
27 WHIPLASH/ or whiplash.mp. (669)
28 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (6521)
29 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (22951)
30 or/21-29 (47422)
31 (acute or emergency or preoperative or postoperative).ti,ab. (134756)
32 30 not 31 (41820)
33 20 or 32 (78648)

34 ketamine/ (2537)
35 (ketamin* or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (4304)
36 34 or 35 (4304)
37 33 and 36 (299)
38 animals/ not humans/ (7371)
39 animal models/ (35864)
40 animal research/ (561)
41 exp rodents/ (224412)
42 (rat or rats or mouse or mice).ti. (122538)
43 or/38-42 (252758)
44 37 not 43 (245)

Scopus, yields 743

((((TITLE (ketamin* OR ketalar OR ketaject OR ketanes OR inducmina OR calipsol OR ketanest OR ketaset OR calypsol OR narkamon OR kalipsol OR velonarcon OR ketava OR ketalin OR ketina OR brevinaze OR esketamine OR norketamine)) OR (ABS (ketamin* OR ketalar OR ketaject OR ketanes OR inducmina OR calipsol OR ketanest OR ketaset OR calypsol OR narkamon OR kalipsol OR velonarcon OR ketava OR ketalin OR ketina OR brevinaze OR esketamine OR norketamine))) AND (TITLE-ABS-KEY ((clinic* W/1 trial*) OR (randomi* W/1 control*) OR (randomi* W/2 trial*) OR (random* W/1 assign*) OR (random* W/1 allocat*) OR (control* W/1 clinic*) OR (control* W/1 trial) OR placebo* OR (quantitat* W/1 stud*) OR (control* W/1 stud*) OR (randomi* W/1 stud*) OR (singl* W/1 blind*) OR (singl* W/1 mask*) OR (doubl* W/1 blind*) OR (doubl* W/1 mask*) OR (tripl* W/1 blind*) OR (tripl* W/1 mask*) OR (trebl* W/1 blind*) OR (trebl* W/1 mask*)) AND NOT (SRCTYPE (b) OR SRCTYPE (k) OR SRCTYPE (p) OR SRCTYPE (r) OR SRCTYPE (d) OR DOCTYPE (ab) OR DOCTYPE (bk) OR DOCTYPE (ch) OR DOCTYPE (bz) OR DOCTYPE (cr) OR DOCTYPE (ed) OR DOCTYPE (er) OR DOCTYPE (le) OR DOCTYPE (no) OR DOCTYPE (pr) OR DOCTYPE (rp) OR DOCTYPE (re) OR DOCTYPE (sh)))) AND (TITLE-ABS-KEY (pain*))) AND ((TITLE-ABS-KEY ((chronic OR back OR discogen* OR bone OR musculoskelet* OR muscle* OR skelet* OR spinal OR spine OR vertebra* OR joint* OR arthritis OR intestin* OR neuropath* OR neck OR cervical* OR head OR facial* OR complex OR radicular OR cervicobrachi* OR orofacial OR somatic OR shoulder* OR knee* OR hip OR hips) W/3 pain)) OR (TITLE-ABS-KEY (backache* OR backpain* OR dorsalgi* OR arthralgi* OR polyarthralgi* OR arthrodyni* OR myalgi* OR fibromyalgi* OR myodyni* OR neuralgi* OR ischialgi* OR crps OR rachialgi* OR whiplash OR headache OR radiculopathy* OR hyperalgesia*)))

CINAHL (EBSCO)

#	Query	
S1	MH randomized controlled trials	127,240
S2	MH double-blind studies	52,678
S3	MH single-blind studies	15,533
S4	MH random assignment	73,255
S5	MH pretest-posttest design	49,013
S6	MH cluster sample	4,953
S7	TI (randomised OR randomized)	126,538
S8	AB (random*)	370,750
S9	TI (trial)	163,177
S10	MH (sample size) AND AB (assigned OR allocated OR control)	4,327
S11	MH (placebos)	13,300
S12	PT (randomized controlled trial)	140,559
S13	AB (control W5 group)	132,613
S14	MH (crossover design) OR MH (comparative studies)	449,659
S15	AB (cluster W3 RCT)	449
S16	MH animals+	99,958
S17	MH (animal studies)	145,806
S18	TI (animal model*)	3,302
S19	S16 OR S17 OR S18	236,925
S20	MH (human)	2,529,605
S21	S19 NOT S20	204,028

S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	948,824
S23	S22 NOT S21	903,548
S24	(MH "Ketamine")	3,774
S25	TI (ketamine or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine) OR AB (ketamine or ketalar or ketaject or ketanes or inducmina or calipsol or ketanest or ketaset or calypsol or narkamon or kalipsol or velonarcon or ketava or ketalin or ketina or brevinaze or esketamine or norketamine)	4,533
S26	S24 OR S25	5,307
S27	S23 AND S26	1,236
S28	TI ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign* or back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) N3 pain*) OR AB ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign* or back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) N3 pain*)	93,332
S29	(MH "Chronic Pain")	25,106
S30	(MH "Osteoarthritis+")	32,091
S31	(MH "Arthritis, Rheumatoid+")	33,555
S32	(MH "Neuralgia")	4,750
S33	(MH "Diabetic Neuropathies")	5,944

S34	(MH "Fibromyalgia")	6,177
S35	(MH "Complex Regional Pain Syndromes") OR (MH "Causalgia") OR (MH "Reflex Sympathetic Dystrophy")	2,284
S36	(MH "Phantom Limb")	653
S37	(MH "Hyperalgesia")	3,727
S38	(MH "Whiplash Injuries")	2,007
S39	TI (headache or osteoarthrit* or osteo-arthrit* or degenrative arthrit* or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*) OR TI (headache or osteoarthrit* or osteo-arthrit* or degenrative arthrit* or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*)	40,240
S40	(MH "Back Pain+")	33,408
S41	(MH "Radiculopathy")	2,487
S42	(MH "Headache")	15,206
S43	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42	214,450
S44	S27 AND S43	188

Table 1. SUCRA values and mean ranks for pain intensity at immediate follow-up time

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	21	0	5.7
Gabapentin	18.8	0	5.9
Ketamine	78.6	3.4	2.3
Ketamine+Opioid	98.9	95.5	1.1
Lidocaine	55.4	0.2	3.7
NSAID	12.4	0	6.3
Opioid	64.8	1	3.1

Table 2. SUCRA values and mean ranks for pain intensity at short follow-up time

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	18.7	0	9.1
Clonidine	71.5	19.8	3.8
Fentanyl+Clonidine	82.5	39.5	2.8
Gabapentin	0.2	0	11
Ketamine+Clonidine	44.3	4.7	6.6
Ketamine	62.2	0.5	4.8
Ketamine+Opioid	86.5	29.2	2.3
Lidocaine	46.8	0.4	6.3
Midazolam	35.5	4.2	7.5
NSAIDs	40	1	7
Opioid	61.7	0.7	4.8

Table 3. SUCRA values and mean ranks for pain intensity at medium follow-up time

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	24	0	7.8
Gabapentin	1.3	0	9.9
Ketamine	62.5	0.9	4.4
Ketamine+Metadone	80.4	27.1	2.8
Ketamine+Opioid	74.3	33.1	3.3
Lidocaine	42.6	1.7	6.2
Methadone	79.8	26.9	2.8
Midazolam	40.8	5.1	6.3
NSAID	50.6	4.5	5.4
Opioid	43.7	0.6	6.1

Table 4. SUCRA values and mean ranks for pain intensity at medium-to-long follow-up time

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	27.4	0.1	7.5
Gabapentin	1.7	0	9.8
Ketamine+Midazolam	58.3	7.4	4.8
Ketamine	59.4	0.5	4.7
Ketamine+Magnesium	42.2	2.5	6.2
Ketamine+Metadone	73.3	14.4	3.4
Lidocaine	29.8	0.7	7.3
Methadone	81	28.7	2.7
Midazolam	73.7	32	3.4
NSAIDs	53.1	13.7	5.2

Table 5. SUCRA values and mean ranks for pain intensity at long follow-up time

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	31.8	0	6.5
Gabapentin	1.5	0	8.9
Ketamine+Midazolam	62.4	3.6	4
Ketamine	62	1.3	4
Ketamine+Metadone	59.3	12.2	4.3
Lidocaine	19	0	7.5
Methadone	69	18.8	3.5
Midazolam	81.8	41.4	2.5
NSAIDs	63	22.6	4

Table 6. Meta regression results for subgroup of low RoB vs. high RoB for pain intensity at immediate follow-up time

Treatment		MD	95% CI		P value
Ketamine	test of interaction	0.15	-1.05	1.34	0.812
	Low RoB	-1.44	-2.54	-0.34	0.010
Gabapentin	test of interaction	.	.	.	.
	Low RoB	0.11	-1.20	1.41	0.874
Ketamine+Opioid	test of interaction	-0.69	-1408.66	1407.29	0.999
	Low RoB	-0.99	-1408.97	1406.97	0.999
Lidocaine	test of interaction	.	.	.	.
	Low RoB	-0.90	-1.52	-0.29	0.004
NSAIDs	test of interaction	.	.	.	.
	Low RoB	0.27	-0.78	1.31	0.619
Opioid	test of interaction	-2.21	-1410.18	1405.77	0.998
	Low RoB	1.03	-1406.94	1409.01	0.999

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 7. Meta regression results for subgroup of mixed pain vs. Other types for pain intensity at immediate follow-up time

Treatment		MD	95% CI		P value
Ketamine	test of interaction	-0.15	-1.34	1.05	0.812
	mixed pain	-1.30	-1.77	-0.82	0.000
Gabapentin	test of interaction	.	.	.	.
	mixed pain	0.11	-1.20	1.41	0.874
Ketamine+Opioid	test of interaction	0.67	-1315.04	1316.38	0.999
	mixed pain	-1.68	-3.00	0.37	0.012
Lidocaine	test of interaction	.	.	.	.
	mixed pain	-0.91	-1.52	-0.29	0.004
NSAIDs	test of interaction	.	.	.	.
	mixed pain	0.12	-1.32	1.56	0.870
Opioid	test of interaction	2.19	-1313.52	1317.89	0.997
	mixed pain	-1.17	-1.80	-0.54	0.000

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 8. Meta regression results for subgroup of neuropathic pain vs. Other types for pain intensity at immediate follow-up time

Treatment		MD	95% CI		P value
Ketamine	test of interaction	0.19	-0.92	1.29	0.743
	neuropathic pain	-1.35	-1.89	-0.79	0.000
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	0.24	-1.41	1.89	0.777
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	-2.17	-3.34	-0.99	0.000
Lidocaine	test of interaction	-0.23	-1.63	1.17	0.746
	neuropathic pain	-0.75	-1.64	0.15	0.104
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	0.21	-1.01	1.44	0.733
Opioid	test of interaction	-0.69	-2.37	0.99	0.420
	neuropathic pain	-0.96	-1.71	-0.22	0.011

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 9. Meta regression results for subgroup of nociceptive pain vs. Other types for pain intensity at immediate follow-up time

Treatment		MD	95% CI		P value
Ketamine	test of interaction	-0.64	-1.81	0.54	0.288
	nociceptive pain	1.20	-1.68	-0.73	0.000
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	0.19	-1.09	1.48	0.766
Ketamine+Opioid	test of interaction	.	.	.	.
	nociceptive pain	-2.21	-3.28	-1.14	0.000
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	-0.86	-1.46	-0.25	0.005
NSAIDs	test of interaction	.	.	.	.
	nociceptive pain	0.36	-0.66	1.37	0.495
Opioid	test of interaction	-0.30	-2.31	1.72	0.774
	nociceptive pain	-1.09	-1.72	-0.45	0.001

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 10. Meta regression results for subgroup of nociplastic pain vs. Other types for pain intensity at immediate follow-up time

Treatment		MD	95% CI		P value
Ketamine	test of interaction	0.35	-0.61	1.30	0.481
	nociplastic pain	-1.47	-2.08	-0.84	0.000
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	-0.06	-1.53	1.39	0.931
Ketamine+Opioid	test of interaction	1.92	-0.57	4.41	0.131
	nociplastic pain	-3.49	-5.54	-1.44	0.001
Lidocaine	test of interaction	0.44	-0.92	1.80	0.525
	nociplastic pain	-1.12	-2.12	-0.12	0.028
NSAIDs	test of interaction	.	.	.	.
	nociplastic pain	0.10	-1.14	1.33	0.880
Opioid	test of interaction	0.47	-0.97	1.90	0.552
	nociplastic pain	-1.45	-2.63	-0.29	0.015

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 11. Meta regression results for subgroup of low RoB vs. high RoB for pain intensity at short

follow-up time

Treatment		MD	95% CI		P value
Clonidine	test of interaction	.	.	.	.
	Low RoB	-1.61	-3.60	0.39	0.114
Fentanyl+Clonidine	test of interaction	.	.	.	.
	Low RoB	-2.01	-3.93	-0.09	0.04
Gabapentin	test of interaction	.	.	.	.
	Low RoB	2.46	0.88	4.05	0.002
Ketamine+Clonidine	test of interaction	.	.	.	.
	Low RoB	-0.71	-2.82	1.41	0.511
Ketamine	test of interaction	0.13	-1.33	1.60	0.859
	Low RoB	-1.37	-2.72	-0.02	0.047
Ketamine+Opioid	test of interaction	-0.92	-1210.32	1208.47	0.999
	Low RoB	-0.74	-1210.14	1208.65	0.999
Lidocaine	test of interaction	.	.	.	.
	Low RoB	-0.93	-1.63	-0.22	0.01
Midazolam	test of interaction	.	.	.	.
	Low RoB	-0.46	-3.00	2.08	0.723
NSAIDs	test of interaction	.	.	.	.
	Low RoB	-0.67	-2.01	0.68	0.33
Opioid	test of interaction	-2.04	-1211.44	1207.35	0.997
	Low RoB	0.75	-1208.65	1210.14	0.999

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 12. Meta regression results for subgroup of mixed pain vs. Other types for pain intensity at short follow-up time

Treatment		MD	95% CI		P value
Clonidine	test of interaction	.	.	.	.
	mixed pain	-1.61	-3.60	0.39	0.114
Fentanyl+Clonidine	test of interaction	.	.	.	.
	mixed pain	-2.01	-3.93	-0.09	0.04
Gabapentin	test of interaction	.	.	.	.
	mixed pain	2.46	0.88	4.05	0.002
Ketamine+Clonidine	test of interaction	.	.	.	.
	mixed pain	-0.71	-2.82	1.41	0.511
Ketamine	test of interaction	-0.13	-1.60	1.33	0.859
	mixed pain	-1.24	-1.81	-0.66	0
Ketamine+Opioid	test of interaction	0.93	-1273.76	1275.62	0.999
	mixed pain	-1.67	-2.90	-0.44	0.008
Lidocaine	test of interaction	.	.	.	.
	mixed pain	-0.93	-1.63	-0.22	0.01
Midazolam	test of interaction	.	.	.	.
	mixed pain	-0.33	-2.56	1.91	0.774
NSAIDs	test of interaction	.	.	.	.
	mixed pain	-0.80	-2.62	1.02	0.388
Opioid	test of interaction	2.05	-1272.64	1276.74	0.997
	mixed pain	-1.30	-2.00	-0.59	0

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 13. Meta regression results for subgroup of neuropathic pain vs. Other types for pain intensity at short follow-up time

Treatment		MD	95% CI		P value
Clonidine	test of interaction	.	.	.	.
	neuropathic pain	-1.70	-3.75	0.35	0.104
Fentanyl+Clonidine	test of interaction	.	.	.	.
	neuropathic pain	-2.10	-4.08	-0.12	0.038
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	2.30	0.44	4.16	0.015
Ketamine+Clonidine	test of interaction	.	.	.	.
	neuropathic pain	-0.80	-2.97	1.37	0.469
Ketamine	test of interaction	-0.18	-1.38	1.03	0.774
	neuropathic pain	-1.22	-1.87	-0.58	0
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	-2.04	-3.18	-0.90	0
Lidocaine	test of interaction	0.17	-1.31	1.65	0.822
	neuropathic pain	-1.05	-2.11	0.00	0.049
Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-0.31	-2.62	1.99	0.79
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	-0.65	-2.11	0.81	0.38
Opioid	test of interaction	0.87	-1.18	2.92	0.407
	neuropathic pain	-1.36	-2.16	-0.56	0.001

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 14. Meta regression results for subgroup of nociceptive pain vs. Other types for pain intensity at short follow-up time

Treatment		MD	95% CI		P value
Clonidine	test of interaction	.	.	.	.
	nociceptive pain	0.06	-2.71	2.82	0.969
Fentanyl+Clonidine	test of interaction	.	.	.	.
	nociceptive pain	-0.34	-3.06	2.37	0.803
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	2.41	0.93	3.90	0.001
Ketamine+Clonidine	test of interaction	.	.	.	.
	nociceptive pain	0.96	-1.90	3.81	0.512
Ketamine	test of interaction	1.49	-0.56	3.53	0.154
	nociceptive pain	-1.29	-1.82	-0.75	0
Ketamine+Opioid	test of interaction	2.14	-0.93	5.21	0.171
	nociceptive pain	-2.18	-3.33	-1.04	0
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	-0.99	-1.64	-0.33	0.003
Midazolam	test of interaction	.	.	.	.
	nociceptive pain	-0.38	-2.54	1.79	0.734
NSAIDs	test of interaction	.	.	.	.
	nociceptive pain	-0.72	-1.94	0.51	0.254
Opioid	test of interaction	2.38	-0.12	4.88	0.062
	nociceptive pain	-1.44	-2.14	-0.75	0

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 15. Meta regression results for subgroup of nociplastic pain vs. Other types for pain intensity at short follow-up time

Treatment		MD	95% CI		P value
Clonidine	test of interaction	.	.	.	.
	nociplastic pain	-1.31	-3.30	0.67	0.195
Fentanyl+Clonidine	test of interaction	.	.	.	.
	nociplastic pain	-1.71	-3.63	0.20	0.079
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	2.55	1.06	4.05	0.001
Ketamine+Clonidine	test of interaction	.	.	.	.
	nociplastic pain	-0.41	-2.52	1.69	0.701
Ketamine	test of interaction	-0.07	-1.03	0.89	0.887
	nociplastic pain	-1.15	-1.80	-0.49	0.001
Ketamine+Opioid	test of interaction	-0.15	-2.23	1.92	0.884
	nociplastic pain	-1.63	-3.19	-0.06	0.041
Lidocaine	test of interaction	-0.39	-1.66	0.88	0.548
	nociplastic pain	-0.81	-1.66	0.03	0.06
Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-0.31	-2.49	1.88	0.785
NSAIDs	test of interaction	.	.	.	.
	nociplastic pain	-0.58	-1.81	0.66	0.361
Opioid	test of interaction	-1.43	-2.83	-0.03	0.056
	nociplastic pain	-0.31	-1.46	0.84	0.594

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 16. Meta regression results for subgroup of low RoB vs. high RoB for pain intensity at medium follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	2.26	0.17	4.35	0.034
Ketamine	test of interaction	-0.92	-1213.37	1211.53	0.999
	Low RoB	-0.42	-1212.87	1212.03	0.999
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	-2.17	-4.32	-0.02	0.048
Ketamine+Opioid	test of interaction	.	.	.	.
	Low RoB	-1.99	-5.03	1.05	0.199
Lidocaine	test of interaction	.	.	.	.
	Low RoB	-0.62	-2.46	1.22	0.51
Methadone	test of interaction	.	.	.	.
	Low RoB	-2.15	-4.35	0.05	0.055
Midazolam	test of interaction	.	.	.	.
	Low RoB	0.43	-1212.02	1212.88	0.999
NSAIDs	test of interaction	.	.	.	.
	Low RoB	-0.96	-3.04	1.12	0.365
Opioid	test of interaction	.	.	.	.
	Low RoB	-0.72	-2.54	1.10	0.438

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 17. Meta regression results for subgroup of mixed pain vs. Other types for pain intensity at medium follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	mixed pain	2.26	0.17	4.35	0.034
Ketamine	test of interaction	1.16	-391.66	393.98	0.995
	mixed pain	-1.34	-2.29	-0.39	0.006
Ketamine+Methadone	test of interaction	.	.	.	.
	mixed pain	-2.17	-4.32	-0.02	0.048
Ketamine+Opioid	test of interaction	.	.	.	.
	mixed pain	-1.99	-5.03	1.05	0.199
Lidocaine	test of interaction	.	.	.	.
	mixed pain	-0.62	-2.46	1.22	0.51
Methadone	test of interaction	.	.	.	.
	mixed pain	-2.15	-4.35	0.05	0.055
Midazolam	test of interaction	.	.	.	.
	mixed pain	-0.49	-3.15	2.17	0.718
NSAIDs	test of interaction	.	.	.	.
	mixed pain	0.19	-392.62	393.01	0.999
Opioid	test of interaction	.	.	.	.
	mixed pain	-0.72	-2.54	1.10	0.438

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 18. Meta regression results for subgroup of neuropathic pain vs. Other types for pain intensity at medium follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	2.88	-0.34	6.10	0.079
Ketamine	test of interaction	0.72	-2.02	3.47	0.605
	neuropathic pain	-1.44	-2.53	-0.36	0.009
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	-1.55	-4.81	1.71	0.351
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	-2.04	-5.24	1.16	0.211
Lidocaine	test of interaction	.	.	.	.
	neuropathic pain	-0.67	-2.64	1.29	0.503
Methadone	test of interaction	.	.	.	.
	neuropathic pain	-1.53	-4.82	1.76	0.362
Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-0.59	-3.40	2.21	0.678
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	-1.06	-3.33	1.20	0.357
Opioid	test of interaction	.	.	.	.
	neuropathic pain	-0.77	-2.72	1.17	0.436

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 19. Meta regression results for subgroup of nociplastic pain vs. Other types for pain intensity at medium follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	2.88	-0.34	6.10	0.079
Ketamine	test of interaction	-0.72	-3.47	2.02	0.605
	nociplastic pain	-0.72	-3.24	1.80	0.575
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	-1.55	-4.80	1.71	0.351
Ketamine+Opioid	test of interaction	.	.	.	.
	nociplastic pain	-2.04	-5.24	1.16	0.211
Lidocaine	test of interaction	.	.	.	.
	nociplastic pain	-0.67	-2.64	1.29	0.503
Methadone	test of interaction	.	.	.	.
	nociplastic pain	-1.53	-4.82	1.76	0.362
Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-0.59	-3.40	2.21	0.678
NSAIDs	test of interaction	.	.	.	.
	nociplastic pain	-0.34	-3.55	2.87	0.835
Opioid	test of interaction	.	.	.	.
	nociplastic pain	-0.77	-2.72	1.17	0.436

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 20. Meta regression results for subgroup of low RoB vs. high RoB for pain intensity at medium-to-long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	1.68	-0.03	3.39	0.055
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	-0.90	-2.25	0.45	0.192
Ketamine	test of interaction	-1.32	-3.49	0.85	0.232
	Low RoB	0.00	-1.88	1.88	1
Ketamine+Magnesium	test of interaction	.	.	.	.
	Low RoB	0.00	-1.72	1.72	1
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	-1.85	-3.65	-0.05	0.043
Lidocaine	test of interaction	.	.	.	.
	Low RoB	0.00	-1.35	1.35	1
Methadone	test of interaction	.	.	.	.
	Low RoB	-2.17	-4.01	-0.34	0.02
Midazolam	test of interaction	.	.	.	.
	Low RoB	-0.68	-3.58	2.22	0.645
NSAIDs	test of interaction	.	.	.	.
	Low RoB	0.21	-2.98	3.40	0.897

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 21. Meta regression results for subgroup of neuropathic pain vs. Other types for pain intensity at medium-to-long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	3.00	0.70	5.30	0.011
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-0.90	-2.25	0.45	0.192
Ketamine	test of interaction	1.32	-0.85	3.49	0.232
	neuropathic pain	-1.32	-2.41	-0.24	0.017
Ketamine+Magnesium	test of interaction	.	.	.	.
	neuropathic pain	0.00	-1.72	1.72	1
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	-0.53	-2.90	1.84	0.661
Lidocaine	test of interaction	.	.	.	.
	neuropathic pain	0.00	-1.35	1.35	1
Methadone	test of interaction	.	.	.	.
	neuropathic pain	-0.85	-3.24	1.54	0.486
Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-2.00	-4.46	0.45	0.11
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	-1.11	-3.90	1.68	0.434

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 22. Meta regression results for subgroup of nociceptive pain vs. Other types for pain intensity at medium-to-long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	2.01	0.18	3.84	0.031
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociceptive pain	-0.90	-2.45	0.65	0.255
Ketamine	test of interaction	0.88	-2264.62	2266.38	0.999
	nociceptive pain	-0.99	-2.00	0.03	0.057
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociceptive pain	-0.42	-2.15	1.30	0.629
Ketamine+Methadone	test of interaction	.	.	.	.
	nociceptive pain	-1.52	-3.43	0.40	0.121
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	0.00	-1.54	1.54	1
Methadone	test of interaction	.	.	.	.
	nociceptive pain	-1.84	-3.78	0.11	0.065
Midazolam	test of interaction	.	.	.	.
	nociceptive pain	-1.67	-4.21	0.87	0.199
NSAIDs	test of interaction	.	.	.	.
	nociceptive pain	0.11	-2265.39	2265.60	1

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 23. Meta regression results for subgroup of nociplastic pain vs. Other types for pain intensity at medium-to-long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	3.00	0.70	5.30	0.011
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-0.90	-2.25	0.45	0.192
Ketamine	test of interaction	-1.32	-3.49	0.85	0.232
	nociplastic pain	0.00	-1.88	1.88	1
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociplastic pain	0.00	-1.72	1.72	1
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	-0.53	-2.90	1.84	0.661
Lidocaine	test of interaction	.	.	.	.
	nociplastic pain	0.00	-1.35	1.35	1
Methadone	test of interaction	.	.	.	.
	nociplastic pain	-0.85	-3.24	1.54	0.486
Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-2.00	-4.46	0.45	0.11
NSAIDs	test of interaction	.	.	.	.
	nociplastic pain	0.21	-2.98	3.40	0.897

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 24. Meta regression results for subgroup of low RoB vs. high RoB for pain intensity at long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	1.61	0.61	2.61	0.002
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	-1.10	-1.71	-0.49	0
Ketamine	test of interaction	-1.57	-1481.15	1478.02	0.998
	Low RoB	0.48	-1479.11	1480.06	0.999
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	-1.19	-4.36	1.99	0.463
Lidocaine	test of interaction	.	.	.	.
	Low RoB	0.40	-0.17	0.97	0.171
Methadone	test of interaction	.	.	.	.
	Low RoB	-1.59	-4.52	1.35	0.289
Midazolam	test of interaction	.	.	.	.
	Low RoB	-0.65	-1480.24	1478.93	0.999
NSAIDs	test of interaction	.	.	.	.
	Low RoB	0.20	-1479.39	1479.79	1

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 25. Meta regression results for subgroup of neuropathic pain vs. Other types for pain intensity at long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	1.48	-602.04	605.00	0.996
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-1.10	-1.71	-0.49	0
Ketamine	test of interaction	-0.13	-603.65	603.39	1
	neuropathic pain	-1.09	-1.86	-0.32	0.006
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	-1.32	-604.85	602.21	0.997
Lidocaine	test of interaction	.	.	.	.
	neuropathic pain	0.40	-0.17	0.97	0.171
Methadone	test of interaction	.	.	.	.
	neuropathic pain	-1.72	-605.25	601.80	0.996
Midazolam	test of interaction	.	.	.	.
	neuropathic pain	-2.22	-4.56	0.12	0.064
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	-1.37	-4.81	2.07	0.435

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 26. Meta regression results for subgroup of nociceptive pain vs. Other types for pain intensity at long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	1.61	0.61	2.61	0.002
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociceptive pain	-1.10	-1.71	-0.49	0
Ketamine	test of interaction	1.23	-3334.89	3337.35	0.999
	nociceptive pain	-1.09	-1.86	-0.32	0.006
Ketamine+Methadone	test of interaction	.	.	.	.
	nociceptive pain	-1.19	-4.36	1.99	0.463
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	0.40	-0.17	0.97	0.171
Methadone	test of interaction	.	.	.	.
	nociceptive pain	-1.59	-4.52	1.35	0.289
Midazolam	test of interaction	.	.	.	.
	nociceptive pain	-2.22	-4.56	0.12	0.064
NSAIDs	test of interaction	.	.	.	.
	nociceptive pain	-0.14	-3336.26	3335.98	1

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 27. Meta regression results for subgroup of nociplastic pain vs. Other types for pain intensity at long follow-up time

Treatment		MD	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	1.52	-575.41	578.46	0.996
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-1.10	-1.71	-0.49	0
Ketamine	test of interaction	0.09	-576.84	577.02	1
	nociplastic pain	-1.18	-578.11	575.76	0.997
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	-1.28	-578.22	575.66	0.997
Lidocaine	test of interaction	.	.	.	.
	nociplastic pain	0.40	-0.17	0.97	0.171
Methadone	test of interaction	.	.	.	.
	nociplastic pain	-1.68	-578.62	575.26	0.995
Midazolam	test of interaction	.	.	.	.
	nociplastic pain	-2.22	-4.56	0.12	0.064
NSAIDs	test of interaction	.	.	.	.
	Low RoB	-1.46	-578.40	575.48	0.996

- MD (95% CI) in front of subgroup are for pain reduction compared to reference (placebo)

-P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (MD=0) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 28. Expanded network estimates of different doses of Ketamine for pain reduction at immediate follow-up time

High dose Ketamine	Medium dose Ketamine	Low dose Ketamine	Gabapentin	Ketamine+Opioid	Lidocaine	NSAIDs	Opioid	Placebo
-0.58 (-2.02,0.87)	-0.36 (-1.41,0.69)	-1.40 (-2.67,-0.13)	2.61 (0.81,4.40)	-1.28 (-2.53,-0.03)	-1.12 (-2.33,0.09)	1.34 (0.09,2.60)	-1.14 (-1.79,-0.48)	
-0.94 (-2.54,0.66)	-0.44 (-1.11,0.24)	-0.07 (-1.18,1.03)	1.33 (-0.36,3.01)	-1.40 (-2.65,0.26)	-0.22 (-0.97,0.54)	1.55 (-0.06,3.15)	-1.06 (-2.13,0.01)	0.22 (-0.58,1.03)
-2.34 (-4.38,-0.30)	-1.76 (-3.41,-0.11)	1.21 (-0.06,2.47)	0.20 (-1.73,2.13)	-2.40 (-3.98,-0.83)	-1.56 (-2.56,-0.56)	0.15 (-0.83,1.12)	0.41 (-1.17,1.99)	-2.20 (-3.33,-1.06)
0.27 (-1.41,1.94)	0.84 (-0.37,2.06)	2.61 (0.81,4.40)	1.33 (-0.36,3.01)	-1.28 (-2.53,-0.03)	-0.44 (-1.11,0.24)	1.21 (-0.06,2.47)	-0.07 (-1.18,1.03)	1.26 (-1.20,3.72)
-1.01 (-2.49,0.46)	-0.44 (-1.11,0.24)	-0.07 (-1.18,1.03)	1.33 (-0.36,3.01)	-1.28 (-2.53,-0.03)	-0.36 (-1.41,0.69)	1.40 (-0.13,2.67)	1.76 (0.11,3.41)	-0.84 (-2.06,0.37)
-2.14 (-3.90,-0.38)	-1.56 (-2.56,-0.56)	-1.20 (-2.65,0.26)	0.20 (-1.73,2.13)	-2.40 (-3.98,-0.83)	-1.12 (-2.33,0.09)	1.34 (0.09,2.60)	-1.14 (-1.79,-0.48)	
-0.79 (-2.12,0.54)	-0.22 (-0.97,0.54)	0.15 (-0.83,1.12)	1.55 (-0.06,3.15)	-1.06 (-2.13,0.01)	0.22 (-0.58,1.03)	1.34 (0.09,2.60)	-1.14 (-1.79,-0.48)	
-1.93 (-3.31,-0.56)	-1.35 (-1.89,-0.81)	-0.99 (-1.93,-0.05)	0.41 (-1.17,1.99)	-2.20 (-3.33,-1.06)	-0.92 (-1.56,-0.27)	0.21 (-0.93,1.35)	-1.14 (-1.79,-0.48)	

Table 29. Expanded network estimates of different delivery methods of Ketamine for pain reduction at immediate follow-up time

IV-Ketamine	IM-Ketamine	Intra articular Ketamine	Ketamine+Opioid	Lidocaine	NSAIDs	Opioid	Placebo
-1.57 (-3.32,0.18)	1.26 (-1.20,3.72)	1.18 (-0.88,3.24)	-1.34 (-2.45,-0.22)	-1.09 (-2.09,-0.10)	1.29 (0.29,2.29)	-1.15 (-1.74,-0.57)	
-0.31 (-2.15,1.52)	2.44 (0.45,4.43)	-0.15 (-2.02,1.71)	-2.43 (-3.74,-1.12)	0.20 (-0.50,0.89)	1.40 (0.13,2.67)	-1.26 (-3.72,1.20)	
0.87 (-0.16,1.90)	1.11 (-0.68,2.89)	-1.25 (-3.25,0.76)	-1.14 (-2.12,-0.15)	-0.96 (-1.51,-0.40)	0.14 (-0.78,1.06)	-1.15 (-1.74,-0.57)	
-0.47 (-1.04,0.11)	0.01 (-1.92,1.94)	0.04 (-1.83,1.92)	-2.29 (-3.32,-1.26)	0.14 (-0.78,1.06)	-1.29 (-2.29,-0.29)	1.15 (0.57,1.74)	
-1.56 (-2.37,-0.75)	1.30 (-0.49,3.10)	-1.11 (-2.89,0.67)	-1.14 (-2.12,-0.15)	0.20 (-0.50,0.89)	1.29 (0.29,2.29)	-1.15 (-1.74,-0.57)	
-0.27 (-0.85,0.31)	0.15 (-1.55,1.85)	-2.29 (-3.32,-1.26)	-0.96 (-1.51,-0.40)	0.14 (-0.78,1.06)	-1.15 (-1.74,-0.57)		
-1.42 (-1.85,-1.00)							

Table 30. Expanded network estimates of different doses of Ketamine for pain reduction at short follow-up time

High-dose Ketamine	Medium-dose Ketamine	Low-dose Ketamine	Gabapentin	Ketamine+Opioid	Lidocaine	Midazolam	NSAIDs	Opioid	Placebo
-1.01 (-2.59,0.57)									
-1.29 (-3.12,0.55)	-0.28 (-1.52,0.96)								
-4.99 (-7.31,-2.66)	-3.98 (-5.87,-2.09)	-3.70 (-5.13,-2.27)							
-0.17 (-1.99,1.65)	0.84 (-0.42,2.10)	1.12 (-0.27,2.51)	4.82 (2.83,6.81)						
-1.31 (-2.93,0.30)	-0.30 (-1.01,0.40)	-0.02 (-1.30,1.25)	3.68 (1.76,5.59)	-1.14 (-2.43,0.15)					
-1.92 (-4.57,0.73)	-0.91 (-3.03,1.21)	-0.63 (-3.09,1.83)	3.07 (0.23,5.91)	-1.75 (-4.22,0.72)	-0.61 (-2.84,1.63)				
-1.58 (-3.54,0.38)	-0.57 (-1.72,0.58)	-0.29 (-1.98,1.40)	3.41 (1.20,5.62)	-1.41 (-3.12,0.30)	-0.27 (-1.62,1.09)	0.34 (-2.08,2.76)			
-0.86 (-2.35,0.64)	0.15 (-0.60,0.91)	0.43 (-0.76,1.62)	4.13 (2.27,5.99)	-0.69 (-1.80,0.43)	0.46 (-0.35,1.26)	1.06 (-1.19,3.32)	0.72 (-0.66,2.10)		
-2.29 (-3.81,-0.78)	-1.28 (-1.90,-0.67)	-1.00 (-2.12,0.11)	2.70 (0.88,4.51)	-2.12 (-3.30,-0.94)	-0.98 (-1.66,-0.29)	-0.37 (-2.58,1.84)	-0.71 (-2.02,0.60)	-1.43 (-2.13,-0.74)	

Table 31. Expanded network estimates of different delivery methods of Ketamine for pain reduction at short follow-up time

IV-Ketamine	IM-Ketamine	Intra articular Ketamine	Transdermal Ketamine	Clonidine	Fentanyl+Clonidine	Ketamine+Clonidine	Ketamine+Opioid	Lidocaine	Midazolam	NSAIDs	Opioid	Placebo
-1.09 (-2.85,0.68)												
-1.62 (-3.68,0.45)	-0.53 (-3.13,2.07)											
0.79 (-1.00,2.57)	1.87 (-0.58,4.32)	2.40 (-0.27,5.08)										
0.89 (-1.33,3.11)	1.97 (-0.81,4.76)	2.50 (-0.48,5.49)	0.10 (-1.90,2.10)									
1.29 (-0.86,3.44)	2.37 (-0.36,5.10)	2.90 (-0.03,5.84)	0.50 (-1.42,2.42)	0.40 (-1.93,2.73)								
-0.01 (-2.34,2.32)	1.07 (-1.80,3.94)	1.60 (-1.46,4.67)	-0.80 (-2.92,1.32)	-0.90 (-3.39,1.59)	-1.30 (-3.73,1.13)							
0.84 (-0.24,1.92)	1.93 (-0.07,3.92)	2.46 (0.19,4.72)	0.05 (-1.66,1.76)	-0.05 (-2.21,2.11)	-0.45 (-2.54,1.65)	0.85 (-1.42,3.13)						
-0.38 (-1.06,0.30)	0.71 (-1.09,2.51)	1.24 (-0.86,3.34)	-1.17 (-3.00,0.67)	-1.27 (-3.53,0.99)	-1.67 (-3.86,0.53)	-0.37 (-2.73,2.00)	-1.22 (-2.40,-0.04)					
-0.91 (-3.02,1.20)	0.18 (-2.58,2.93)	0.71 (-2.25,3.66)	-1.70 (-4.47,1.07)	-1.80 (-4.86,1.27)	-2.20 (-5.22,0.82)	-0.90 (-4.04,2.25)	-1.75 (-4.13,0.63)	-0.53 (-2.75,1.69)				
-0.57 (-1.71,0.56)	0.52 (-1.58,2.62)	1.05 (-1.31,3.41)	-1.36 (-3.47,0.76)	-1.46 (-3.95,1.03)	-1.86 (-4.29,0.58)	-0.56 (-3.15,2.03)	-1.41 (-2.98,0.16)	-0.19 (-1.51,1.13)	0.34 (-2.06,2.74)			
0.02 (-0.65,0.68)	1.10 (-0.70,2.91)	1.63 (-0.47,3.73)	-0.77 (-2.46,0.92)	-0.87 (-3.02,1.27)	-1.27 (-3.35,0.80)	0.03 (-2.23,2.28)	-0.82 (-1.82,0.17)	0.39 (-0.38,1.17)	0.93 (-1.29,3.14)	0.59 (-0.73,1.90)		
-1.42 (-1.99,-0.84)	-0.33 (-2.00,1.34)	0.20 (-1.79,2.19)	-2.20 (-4.00,-0.41)	-2.30 (-4.53,-0.08)	-2.70 (-4.86,-0.55)	-1.40 (-3.74,0.93)	-2.26 (-3.35,-1.16)	-1.04 (-1.71,-0.36)	-0.51 (-2.70,1.68)	-0.85 (-2.12,0.42)	-1.43 (-2.12,-0.75)	

Table 32. Expanded network estimates of different doses of Ketamine for pain reduction at medium follow-up time

High dose Ketamine	Medium dose Ketamine	Low dose Ketamine	Gabapentin	Ketamine+Methadone	Ketamine+Opioid	Lidocaine	Methadone	Midazolam	NSAIDs	Opioid	Placebo
-0.03 (-4.02,3.96)	1.17 (-1.68,4.02)	-3.60 (-5.86,-1.34)	4.43 (1.19,7.67)	-1.03 (-5.62,3.55)	-1.37 (-5.03,2.29)	2.38 (-1.33,6.09)	-2.83 (-7.47,1.80)	-2.36 (-6.69,1.97)	0.47 (-3.12,4.06)	0.08 (-3.21,3.37)	-0.40 (-2.80,2.00)
1.14 (-2.39,4.67)	-2.43 (-6.06,1.21)	0.83 (-1.49,3.15)	-2.40 (-6.08,1.28)	-0.02 (-2.39,2.35)	-2.85 (-7.47,1.76)	-2.38 (-6.69,1.92)	-2.30 (-5.97,1.37)	-2.40 (-6.08,1.28)	-2.38 (-6.69,1.92)	-2.36 (-6.69,1.97)	-2.70 (-5.48,0.07)
-2.46 (-6.65,1.74)	2.00 (-1.67,5.68)	-0.20 (-4.16,3.75)	2.03 (-1.62,5.67)	1.01 (-3.59,5.62)	-1.82 (-6.42,2.78)	-1.35 (-5.64,2.94)	-1.27 (-4.02,1.48)	-1.37 (-5.03,2.29)	-1.03 (-5.62,3.55)	-1.03 (-5.62,3.55)	-1.67 (-5.32,1.98)
1.97 (-2.25,6.20)	0.97 (-2.68,4.62)	-1.57 (-4.43,1.29)	4.41 (1.14,7.68)	2.38 (-1.33,6.09)	-0.45 (-4.15,3.25	0.02 (-3.28,3.32)	0.10 (-2.31,2.51)	0.02 (-3.28,3.32)	-2.40 (-6.08,1.28)	-2.40 (-6.08,1.28)	-0.30 (-2.72,2.12
0.94 (-3.91,5.79)	-0.40 (-2.82,2.02)	0.81 (-1.55,3.17)	1.58 (-3.01,6.16)	-0.45 (-4.15,3.25	-2.83 (-7.47,1.80)	-2.36 (-6.69,1.97)	-2.28 (-5.98,1.41)	-2.83 (-7.47,1.80)	-2.83 (-7.47,1.80)	-2.83 (-7.47,1.80)	-2.68 (-5.49,0.13)
-0.43 (-4.43,3.57)	1.98 (-1.72,5.68)	-2.02 (-6.01,1.97)	2.05 (-2.23,6.32)	-2.83 (-7.47,1.80)	-2.36 (-6.69,1.97)	0.47 (-3.12,4.06)	0.55 (-3.13,4.23)	0.47 (-3.12,4.06)	0.47 (-3.12,4.06)	0.47 (-3.12,4.06)	0.15 (-3.54,3.84)
1.95 (-2.29,6.20)	-0.85 (-3.64,1.94)	-1.55 (-5.18,2.08)	2.13 (-1.51,5.76)	-2.40 (-6.08,1.28)	-2.38 (-6.69,1.92)	-2.38 (-6.69,1.92)	-2.30 (-5.97,1.37)	-2.38 (-6.69,1.92)	-2.36 (-6.69,1.97)	-2.38 (-6.69,1.92)	-2.38 (-6.69,1.92)
-0.88 (-5.75,3.99)	-0.38 (-2.63,1.87)	-1.47 (-4.32,1.37)	1.73 (-1.00,4.45)	-2.36 (-6.69,1.97)	-2.40 (-6.08,1.28)	-2.40 (-6.08,1.28)	-2.38 (-6.69,1.92)	-2.40 (-6.08,1.28)	-2.40 (-6.08,1.28)	-2.40 (-6.08,1.28)	-2.40 (-6.08,1.28)
-0.41 (-4.99,4.17)	-0.30 (-2.70,2.10)	-1.87 (-3.40,-0.35)	2.70 (-5.48,0.07)	-2.38 (-6.69,1.92)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)	-2.36 (-6.69,1.97)
-0.33 (-4.32,3.66)	-0.70 (-3.11,1.71)	1.87 (-3.40,-0.35)	1.73 (-1.00,4.45)	-2.70 (-5.48,0.07)	-1.67 (-5.32,1.98)	-0.30 (-2.72,2.12	-2.68 (-5.49,0.13)	0.15 (-3.54,3.84)	-0.32 (-3.61,2.97)	-0.40 (-2.80,2.00)	
-0.73 (-3.92,2.46)											

Table 33. Expanded network estimates of different delivery methods of Ketamine for pain reduction at medium follow-up time

IV Ketamine	Transdermal Ketamine	Ketamine+Opioid	Lidocaine	Midazolam	NSAIDs	Opioid	Placebo
-0.72 (-3.47,2.02)	1.32 (-2.75,5.39)	-1.37 (-4.71,1.97)	-0.08 (-3.33,3.17)	0.47 (-2.79,3.73)	-0.29 (-3.07,2.49)	-0.77 (-2.72,1.17)	
0.60 (-2.60,3.80)	-0.05 (-3.24,3.15)	-1.45 (-5.56,2.66)	0.39 (-2.40,3.19)	0.18 (-3.06,3.41)	-1.06 (-3.33,1.20)		
-0.77 (-2.74,1.19)	-0.13 (-3.90,3.64)	-0.98 (-4.74,2.79)	0.10 (-2.07,2.27)	-0.59 (-3.40,2.21)			
-0.85 (-3.44,1.74)	0.34 (-3.04,3.73)	-1.27 (-3.81,1.27)	-0.67 (-2.64,1.29)				
-0.38 (-2.36,1.60)	0.05 (-3.13,3.23)	-2.04 (-5.24,1.16)					
-0.67 (-2.62,1.27)	-0.72 (-3.24,1.80)						
-1.44 (-2.53,-0.36)							

Table 34. Network estimates pain reduction at immediate follow-up time by excluding stand-alone nodes

Ketamine				
0.92 (-0.13,1.97)	Ketamine+Opioid			
-0.41 (-1.00,0.17)	-1.34 (-2.48,-0.20)	Lidocaine		
-0.22 (-0.80,0.37)	-1.14 (-2.14,-0.14)	0.20 (-0.52,0.91)	Opioid	
-1.32 (-1.73,-0.90)	-2.24 (-3.29,-1.19)	-0.90 (-1.48,-0.33)	-1.10 (-1.69,-0.51)	Placebo

Table 35. Network estimates pain reduction at short follow-up time by excluding stand-alone nodes

Ketamine							
0.41 (-1.49,2.31)	Clonidine						
0.81 (-1.01,2.63)	0.40 (-1.94,2.74)	Fentanyl+Clonidine					
-0.49 (-2.51,1.53)	-0.90 (-3.40,1.60)	-1.30 (-3.74,1.14)	Ketamine+Clonidine				
0.74 (-0.27,1.74)	0.33 (-1.70,2.36)	-0.07 (-2.03,1.89)	1.23 (-0.92,3.38)	Ketamine+Opioid			
-0.32 (-0.98,0.35)	-0.73 (-2.72,1.27)	-1.13 (-3.05,0.79)	0.17 (-1.94,2.29)	-1.06 (-2.19,0.08)	Lidocaine		
0.00 (-0.63,0.63)	-0.41 (-2.35,1.52)	-0.81 (-2.67,1.05)	0.49 (-1.57,2.55)	-0.74 (-1.72,0.24)	0.32 (-0.45,1.09)	Opioid	
-1.25 (-1.76,-0.74)	-1.66 (-3.61,0.29)	-2.06 (-3.93,-0.19)	-0.76 (-2.83,1.31)	-1.99 (-3.03,-0.95)	-0.93 (-1.60,-0.26)	-1.25 (-1.91,-0.59)	Placebo

Table 36. Network estimates pain reduction at medium follow-up time by excluding stand-alone nodes

Ketamine						
0.65 (-2.39,3.69)	Ketamine+Opioid					
-0.72 (-2.56,1.12)	-1.37 (-4.55,1.81)	Lidocaine				
-0.62 (-2.44,1.20)	-1.27 (-3.70,1.16)	0.10 (-1.95,2.15)	Opioid			
0.83 (-1.10,2.76)	0.18 (-3.42,3.78)	1.55 (-1.12,4.22)	1.45 (-1.20,4.10)	Ketamine+Methadone		
0.81 (-1.17,2.79)	0.16 (-3.47,3.79)	1.53 (-1.18,4.24)	1.43 (-1.26,4.12)	-0.02 (-2.02,1.98)	Methadone	
-1.34 (-2.29,-0.39)	-1.99 (-5.03,1.05)	-0.62 (-2.46,1.22)	-0.72 (-2.54,1.10)	-2.17 (-4.32,-0.02)	-2.15 (-4.35,0.05)	placebo

Table 37. Network estimates pain reduction at medium-to-long follow-up time by excluding stand-alone nodes

Ketamine						
-0.09 (-1.94,1.77)	Ketamine+Midazolam					
-0.56 (-2.33,1.21)	-0.48 (-2.79,1.84)	Ketamine+Magnesium				
0.53 (-1.09,2.15)	0.62 (-1.85,3.08)	1.09 (-1.31,3.49)	Ketamine+Methadone			
-0.99 (-2.83,0.86)	-0.90 (-2.45,0.65)	-0.42 (-2.74,1.89)	-1.52 (-3.98,0.94)	Lidocaine		
0.85 (-0.81,2.51)	0.94 (-1.55,3.42)	1.41 (-1.02,3.84)	0.32 (-1.32,1.96)	1.84 (-0.65,4.32)	Methadone	
-0.99 (-2.00,0.03)	-0.90 (-2.45,0.65)	-0.42 (-2.15,1.30)	-1.52 (-3.43,0.40)	0.00 (-1.54,1.54)	-1.84 (-3.78,0.11)	Placebo

Table 38. Network estimates pain reduction at long follow-up time by excluding stand-alone nodes

Ketamine					
0.01 (-0.97,0.99)	**Ketamine+Midazolam**				
0.10 (-2.98,3.18)	0.09 (-3.14,3.32)	**Ketamine+Methadone**			
-1.49 (-2.45,-0.53)	-1.50 (-2.05,-0.95)	-1.59 (-4.82,1.64)	**Lidocaine**		
0.50 (-2.33,3.33)	0.49 (-2.51,3.49)	0.40 (-2.00,2.80)	1.99 (-1.00,4.98)	**Methadone**	
-1.09 (-1.86,-0.32)	-1.10 (-1.71,-0.49)	-1.19 (-4.36,1.99)	0.40 (-0.17,0.97)	-1.59 (-4.52,1.35)	**Placebo**

Table 39. SUCRA values and mean ranks for physical function

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	74.7	23.1	2.5
Ketamine+Midazolam	37.3	7.7	4.8
Ketamine	40.2	1.6	4.6
Ketamine+Magnesium	56.5	20.6	3.6
Lidocaine	51.9	9	3.9
Midazolam	53.6	29.9	3.8
Opioid	35.8	8	4.9

Table 40. SUCRA values and mean ranks for incidence of GI adverse events

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	91.5	37.1	1.8
Gabapentin	82.9	54.1	2.5
Ketamine+Midazolam	62	5	4.4
Ketamine	54.4	0	5.1
Ketamine+Magnesium	54.1	1.5	5.1
Ketamine+Methadone	27.5	0.6	7.5
Ketamine+Opioid	15.2	0	8.6
Lidocaine	64.8	1.2	4.2
Methadone	18.6	0.4	8.3
Opioid	28.9	0	7.4

Table 41. SUCRA values and mean ranks for incidence of dizziness

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
placebo	77.8	21	2.6
Ketamine+Midazolam	48.2	9.2	4.6
Ketamine	31.1	0.1	5.8
Ketamine+Magnesium	18.7	2.1	6.7
Ketamine+Methadone	75.6	48.4	2.7
Lidocaine	45.6	5.2	4.8
Methadone	52.6	12.6	4.3
Opioid	50.4	1.5	4.5

Table 42. SUCRA values and mean ranks for incidence of fatigue, somnolence, and sedation

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	96.8	74.9	1.3
Ketamine+Midazolam	26.3	0	6.9
Ketamine	62.7	0	4
Ketamine+Magnesium	80.8	24.5	2.5
Ketamine+Methadone	22.6	0.4	7.2
Ketamine+Opioid	37.3	0	6
Lidocaine	78.3	0.1	2.7
Methadone	1.3	0	8.9
Opioid	43.8	0	5.5

Table 43. Definition of dissociative symptoms among included studies

Study	Dissociative symptoms definition
Mitchell 2002	Increased emotionality
Sorensen 1995	Feeling of unreality
Peter 2023	Giddiness
Lemming 2007	Dreams, Hallucinations
Max 1995	Dissociation
Muller 2005	Feeling of drunkenness
Vranken 2005	Confusion, Vivid dreams
Kvarnstorm 2004	Out of body sensation
Kvarnstorm 2003	Out of body sensation
Lumanauw 2019	Hallucinations
Pickering 2020	Feeling of drunkenness
Eide 1994	Feeling of unreality
Rigo 2017	Hallucination
Sorensen 1997	Dissociative Effects
Rabben 1999	Hallucinations, Feeling of insobriety
Jørum 2002	Feeling intoxicated, Feeling of unreality
Sigtermans 2009	Psychomimetic effects

Table 44. SUCRA values and mean ranks for incidence of dissociative symptoms

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	83.9	23.1	2.4
Gabapentin	0.9	0	9.9
Ketamine+Midazolam	36.2	0.2	6.7
Ketamine	30.1	0	7.3
Ketamine+Magnesium	49.7	7.2	5.5
Ketamine+Methadone	67.9	31.2	3.9
Ketamine+Opioid	35.6	1.1	6.8
Lidocaine	63.6	3.2	4.3
Methadone	67	31.1	4
Opioid	65.1	2.7	4.1

Table 45. SUCRA values and mean ranks for incidence of visual impairment

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	92.7	66.3	1.4
Gabapentin	16.2	1.6	6
Ketamine+Midazolam	31.2	0.1	5.1
Ketamine	28.9	0	5.3
Lidocaine	79.4	23.2	2.2
NSAIDs	34.3	4.5	4.9
Opioid	67.2	4.2	3

Table 46. Meta regression results for subgroup of low RoB vs. high RoB for incidence of GI adverse events

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	0.79	0.04	16.63	0.881
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	2.98	0.53	16.78	0.216
Ketamine	test of interaction	0.99	0.16	6.27	0.994
	Low RoB	3.99	0.71	22.49	0.117
Ketamine+Magnesium	test of interaction	.	.	.	.
	Low RoB	3.74	0.55	25.59	0.179
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	10.06	1.10	91.74	0.041
Ketamine+Opioid	test of interaction	.	.	.	.
	Low RoB	11.61	3.89	34.65	0
Lidocaine	test of interaction	.	.	.	.
	Low RoB	2.80	0.89	8.84	0.079
Methadone	test of interaction	.	.	.	.
	Low RoB	13.41	1.58	113.63	0.017
Opioid	test of interaction	.	.	.	.
	Low RoB	7.45	3.44	16.00	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 47. Meta regression results for subgroup of mixed pain vs. Other types for incidence of GI adverse events

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	mixed pain	0.78	0.04	16.18	0.87
Ketamine+Midazolam	test of interaction	.	.	.	.
	mixed pain	2.92	0.52	16.34	0.222
Ketamine	test of interaction	1.68	0.09	30.82	0.728
	mixed pain	3.88	2.10	7.16	0
Ketamine+Magnesium	test of interaction	.	.	.	.
	mixed pain	3.65	0.84	15.84	0.083
Ketamine+Methadone	test of interaction	.	.	.	.
	mixed pain	9.84	1.09	89.08	0.042
Ketamine+Opioid	test of interaction	.	.	.	.
	mixed pain	11.39	3.86	33.64	0
Lidocaine	test of interaction	.	.	.	.
	mixed pain	2.75	0.88	8.59	0.082
Methadone	test of interaction	.	.	.	.
	mixed pain	13.12	1.56	110.31	0.018
Opioid	test of interaction	.	.	.	.
	mixed pain	7.30	3.43	15.55	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 48. Meta regression results for subgroup of neuropathic pain vs. Other types for incidence of GI adverse events

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	0.78	0.03	17.88	0.875
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	2.46	0.37	16.42	0.354
Ketamine	test of interaction	0.98	0.28	3.40	0.978
	neuropathic pain	3.96	1.86	8.43	0
Ketamine+Magnesium	test of interaction	.	.	.	.
	neuropathic pain	3.67	0.75	17.83	0.108
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	9.88	0.96	101.91	0.054
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	14.91	4.21	52.81	0
Lidocaine	test of interaction	.	.	.	.
	neuropathic pain	2.76	0.74	10.26	0.13
Methadone	test of interaction	.	.	.	.
	neuropathic pain	13.17	1.37	126.74	0.026
Opioid	test of interaction	0.60	0.13	2.83	0.516
	neuropathic pain	10.28	3.43	30.75	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 49. Meta regression results for subgroup of nociceptive pain vs. Other types for incidence of GI adverse events

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	0.80	0.04	16.62	0.885
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociceptive pain	2.87	0.51	16.01	0.23
Ketamine	test of interaction	0.09	0.00	.	0.998
	nociceptive pain	3.99	2.19	7.27	0
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociceptive pain	3.74	0.87	16.15	0.077
Ketamine+Methadone	test of interaction	.	.	.	.
	nociceptive pain	10.14	1.12	91.44	0.039
Ketamine+Opioid	test of interaction	.	.	.	.
	nociceptive pain	11.28	3.84	33.20	0
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	2.82	0.91	8.76	0.073
Methadone	test of interaction	.	.	.	.
	nociceptive pain	13.52	1.61	113.22	0.016
Opioid	test of interaction	0.40	0.00	.	0.999
	nociceptive pain	7.17	3.38	15.20	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 50. Meta regression results for subgroup of nociplastic pain vs. Other types for incidence of GI adverse events

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	0.81	0.04	18.30	0.895
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	2.74	0.42	17.83	0.293
Ketamine	test of interaction	0.95	0.28	3.22	0.939
	nociplastic pain	4.05	1.60	10.27	0.003
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociplastic pain	3.78	0.79	18.03	0.095
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	10.28	1.02	103.72	0.048
Ketamine+Opioid	test of interaction	.	.	.	.
	nociplastic pain	13.47	3.71	48.88	0
Lidocaine	test of interaction	.	.	.	.
	nociplastic pain	2.85	0.79	10.31	0.11
Methadone	test of interaction	.	.	.	.
	nociplastic pain	13.71	1.46	128.90	0.022
Opioid	test of interaction	1.33	0.28	6.26	0.722
	nociplastic pain	6.84	2.37	19.71	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 51. Meta regression results for subgroup of low RoB vs. high RoB for incidence of dizziness

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	2.48	0.17	36.39	0.509
Ketamine	test of interaction	1.16	0.08	17.98	0.914
	Low RoB	3.25	0.28	36.98	0.343
Ketamine+Magnesium	test of interaction	.	.	.	.
	Low RoB	9.01	0.39	209.79	0.171
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	0.65	0.01	29.63	0.824
Lidocaine	test of interaction	.	.	.	.
	Low RoB	2.68	0.32	22.48	0.363
Methadone	test of interaction	.	.	.	.
	Low RoB	1.94	0.09	42.35	0.673
Opioid	test of interaction	.	.	.	.
	Low RoB	2.34	0.46	11.89	0.306

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 52. Meta regression results for subgroup of mixed pain vs. Other types for incidence of dizziness

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	mixed pain	2.29	0.16	33.31	0.546
Ketamine	test of interaction	1.58	0.07	36.92	0.775
	mixed pain	3.42	1.03	11.39	0.045
Ketamine+Magnesium	test of interaction	.	.	.	.
	mixed pain	9.25	0.48	179.93	0.142
Ketamine+Methadone	test of interaction	.	.	.	.
	mixed pain	0.59	0.01	26.53	0.784
Lidocaine	test of interaction	.	.	.	.
	mixed pain	2.48	0.30	20.42	0.4
Methadone	test of interaction	.	.	.	.
	mixed pain	1.76	0.08	37.81	0.718
Opioid	test of interaction	.	.	.	.
	mixed pain	2.16	0 .4335256	10.74	0.348

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 53. Meta regression results for subgroup of neuropathic pain vs. Other types for incidence of dizziness

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	2.89	0.18	45.24	0.45
Ketamine	test of interaction	0.61	0.07	5.41	0.655
	neuropathic pain	5.06	0.98	26.12	0.053
Ketamine+Magnesium	test of interaction	.	.	.	.
	neuropathic pain	8.76	0.47	162.55	0.145
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	0.53	0.01	23.97	0.742
Lidocaine	test of interaction	0.05	0.00	3.61	0.174
	neuropathic pain	10.20	0.46	225.25	0.141
Methadone	test of interaction	.	.	.	.
	neuropathic pain	1.58	0.07	34.21	0.771
Opioid	test of interaction	1.19	0.04	34.63	0.919
	neuropathic pain	2.29	0.14	36.90	0.56

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 54. Meta regression results for subgroup of nociplastic pain vs. Other types for incidence of dizziness

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	3.18	0.21	47.70	0.402
Ketamine	test of interaction	1.41	0.13	15.56	0.779
	nociplastic pain	3.46	0.96	12.51	0.059
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociplastic pain	9.30	0.51	170.32	0.133
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	0.59	0.01	25.66	0.786
Lidocaine	test of interaction	16.36	0.22	1237.58	0.205
	nociplastic pain	0.60	0.04	9.88	0.723
Methadone	test of interaction	.	.	.	.
	nociplastic pain	1.78	0.09	36.16	0.708
Opioid	test of interaction	0.74	0.02	24.08	0.864
	nociplastic pain	3.01	0.49	18.32	0.233

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 55. Meta regression results for subgroup of low RoB vs. high RoB for incidence of fatigue, somnolence, and sedation

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	5.09	2.62	9.86	0
Ketamine	test of interaction	2.38	0.56	10.08	0.239
	Low RoB	1.33	0.34	5.21	0.679
Ketamine+Magnesium	test of interaction	.	.	.	.
	Low RoB	1.00	0.23	4.37	1
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	8.06	1.86	34.82	0.005
Ketamine+Opioid	test of interaction	.	.	.	.
	Low RoB	4.15	2.52	6.82	0
Lidocaine	test of interaction	.	.	.	.
	Low RoB	2.30	1.33	3.98	0.003
Methadone	test of interaction	.	.	.	.
	Low RoB	16.11	4.18	62.15	0
Opioid	test of interaction	.	.	.	.
	Low RoB	3.96	2.41	6.50	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 56. Meta regression results for subgroup of neuropathic pain vs. Other types for incidence of fatigue, somnolence, and sedation

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	2.33	0.95	5.70	0.064
Ketamine	test of interaction	0.69	0.25	1.89	0.47
	neuropathic pain	3.87	1.63	9.17	0.002
Ketamine+Magnesium	test of interaction	.	.	.	.
	neuropathic pain	1.50	0.42	5.39	0.534
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	6.76	1.54	29.72	0.011
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	5.28	2.28	12.24	0
Lidocaine	test of interaction	0.89	0.24	3.27	0.855
	neuropathic pain	2.28	0.72	7.27	0.164
Methadone	test of interaction	.	.	.	.
	neuropathic pain	13.52	3.44	53.13	0
Opioid	test of interaction	0.35	0.11	1.11	0.075
	neuropathic pain	5.15	2.21	11.97	0

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 57. Meta regression results for subgroup of nociplastic pain vs. Other types for incidence of fatigue, somnolence, and sedation

Treatment		RR	95% CI		P value
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	2.33	0.95	5.70	0.064
Ketamine	test of interaction	1.45	0.53	3.99	0.47
	nociplastic pain	2.66	1.57	4.51	0
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociplastic pain	1.50	0.42	5.39	0.534
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	6.76	1.54	29.72	0.011
Ketamine+Opioid	test of interaction	.	.	.	.
	nociplastic pain	5.28	2.28	12.24	0
Lidocaine	test of interaction	1.13	0.31	4.17	0.855
	nociplastic pain	2.02	1.11	3.68	0.022
Methadone	test of interaction	.	.	.	.
	nociplastic pain	13.52	3.44	53.13	0
Opioid	test of interaction	2.84	0.90	8.97	0.075
	nociplastic pain	1.81	0.83	3.95	0.135

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 58. Meta regression results for subgroup of low RoB vs. high RoB for incidence of dissociative symptoms

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	151.08	7.77	2937.79	0.001
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	3.82	0.93	15.77	0.064
Ketamine	test of interaction	1.22	0.12	12.31	0.868
	Low RoB	3.55	0.39	32.18	0.26
Ketamine+Magnesium	test of interaction	.	.	.	.
	Low RoB	2.26	0.15	34.75	0.557
Ketamine+Methadone	test of interaction	.	.	.	.
	Low RoB	1.23	0.05	33.59	0.901
Ketamine+Opioid	test of interaction	.	.	.	.
	Low RoB	4.07	0.76	21.83	0.102
Lidocaine	test of interaction	.	.	.	.
	Low RoB	1.80	0.60	5.40	0.294
Methadone	test of interaction	.	.	.	.
	Low RoB	1.23	0.05	33.59	0.901
Opioid	test of interaction	.	.	.	.
	Low RoB	1.83	0.66	5.12	0.247

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 59. Meta regression results for subgroup of mixed pain vs. Other types for incidence of dissociative symptoms

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	mixed pain	152.01	7.87	2935.84	0.001
Ketamine+Midazolam	test of interaction	.	.	.	.
	mixed pain	3.84	0.94	15.64	0.06
Ketamine	test of interaction	0.58	0.02	14.20	0.736
	mixed pain	4.34	2.19	8.60	0
Ketamine+Magnesium	test of interaction	.	.	.	.
	mixed pain	2.67	0.32	22.29	0.364
Ketamine+Methadone	test of interaction	.	.	.	.
	mixed pain	1.24	0.05	33.59	0.898
Ketamine+Opioid	test of interaction	.	.	.	.
	mixed pain	4.09	0.77	21.77	0.099
Lidocaine	test of interaction	.	.	.	.
	mixed pain	1.81	0.61	5.36	0.284
Methadone	test of interaction	.	.	.	.
	mixed pain	1.24	0.05	33.59	0.898
Opioid	test of interaction	.	.	.	.
	mixed pain	1.84	0.67	5.09	0.237

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 60. Meta regression results for subgroup of neuropathic pain vs. Other types for incidence of dissociative symptoms

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	216.12	9.39	4974.18	0.001
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	5.95	0.90	39.46	0.065
Ketamine	test of interaction	1.72	0.41	7.29	0.46
	neuropathic pain	3.58	1.60	8.02	0.002
Ketamine+Magnesium	test of interaction	.	.	.	.
	neuropathic pain	3.56	0.36	35.04	0.276
Ketamine+Methadone	test of interaction	.	.	.	.
	neuropathic pain	1.76	0.06	55.95	0.747
Ketamine+Opioid	test of interaction	.	.	.	.
	neuropathic pain	3.04	0.48	19.09	0.237
Lidocaine	test of interaction	13.95	0.49	399.25	0.124
	neuropathic pain	0.22	0.01	4.52	0.326
Methadone	test of interaction	.	.	.	.
	neuropathic pain	1.76	0.06	55.95	0.747
Opioid	test of interaction	2.21	0.27	18.34	0.464
	neuropathic pain	1.29	0.32	5.21	0.717

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 61. Meta regression results for subgroup of nociplastic pain vs. Other types for incidence of dissociative symptoms

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	192.81	8.56	4344.21	0.001
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	5.35	0.82	34.68	0.079
Ketamine	test of interaction	0.67	0.16	2.71	0.572
	nociplastic pain	5.51	1.79	16.91	0.003
Ketamine+Magnesium	test of interaction	.	.	.	.
	nociplastic pain	3.25	0.34	31.34	0.309
Ketamine+Methadone	test of interaction	.	.	.	.
	nociplastic pain	1.57	0.05	48.96	0.796
Ketamine+Opioid	test of interaction	.	.	.	.
	nociplastic pain	3.10	0.48	19.88	0.232
Lidocaine	test of interaction	0.08	0.00	2.33	0.143
	nociplastic pain	2.76	0.67	11.44	0.161
Methadone	test of interaction	.	.	.	.
	nociplastic pain	1.57	0.05	48.96	0.796
Opioid	test of interaction	0.52	0.06	4.22	0.537
	nociplastic pain	2.57	0.54	12.12	0.234

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 62. Meta regression results for subgroup of low RoB vs. high RoB for incidence of visual impairment

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	Low RoB	30.62	1.03	908.88	0.048
Ketamine+Midazolam	test of interaction	.	.	.	.
	Low RoB	9.67	1.59	58.67	0.014
Ketamine	test of interaction	10.36	0.00	.	0.998
	Low RoB	0.99	0.00	.	1
Lidocaine	test of interaction	.	.	.	.
	Low RoB	1.73	0.27	11.00	0.559
NSAIDs	test of interaction	.	.	.	.
	Low RoB	0.99	0.00	.	1
Opioid	test of interaction	.	.	.	.
	Low RoB	3.02	0.61	14.86	0.174

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 63. Meta regression results for subgroup of neuropathic pain vs. Other types for incidence of visual impairment

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	neuropathic pain	34.87	1.12	1081.65	0.043
Ketamine+Midazolam	test of interaction	.	.	.	.
	neuropathic pain	7.65	0.97	60.49	0.054
Ketamine	test of interaction	11.62	0.20	669.47	0.236
	neuropathic pain	1.00	0.02	45.13	1
Lidocaine	test of interaction	.	.	.	.
	neuropathic pain	1.97	0.29	13.43	0.491
NSAIDs	test of interaction	.	.	.	.
	neuropathic pain	1.00	0.01	106.72	1
Opioid	test of interaction	0.80	0.02	29.14	0.902
	neuropathic pain	3.00	0.14	64.26	0.482

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 64. Meta regression results for subgroup of nociceptive pain vs. Other types for incidence of visual impairment

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociceptive pain	30.62	1.03	908.88	0.048
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociceptive pain	9.67	1.59	58.67	0.014
Ketamine	test of interaction	0.10	0.00	.	0.999
	nociceptive pain	10.21	2.86	36.42	0
Lidocaine	test of interaction	.	.	.	.
	nociceptive pain	1.73	0.27	11.00	0.559
NSAIDs	test of interaction	.	.	.	.
	nociceptive pain	1.00	0.00	.	1
Opioid	test of interaction	.	.	.	.
	nociceptive pain	3.02	0.61	14.86	0.174

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 65. Meta regression results for subgroup of nociplastic pain vs. Other types for incidence of visual impairment

Treatment		RR	95% CI		P value
Gabapentin	test of interaction	.	.	.	.
	nociplastic pain	34.87	1.12	1081.65	0.043
Ketamine+Midazolam	test of interaction	.	.	.	.
	nociplastic pain	7.65	0.97	60.49	0.054
Ketamine	test of interaction	0.09	0.00	4.96	0.236
	nociplastic pain	11.62	2.91	46.45	0.001
Lidocaine	test of interaction	.	.	.	.
	nociplastic pain	1.97	0.29	13.43	0.491
NSAIDs	test of interaction	.	.	.	.
	nociplastic pain	11.62	0.56	242.02	0.113
Opioid	test of interaction	1.25	0.03	45.87	0.902
	nociplastic pain	2.39	0.36	15.78	0.365

- RR (95% CI) in front of subgroup are for incidence of adverse events compared to reference (placebo)

- P values highlighted in orange are for test of interaction

-P values in white cells are for test of null value (RR=1) for the effect estimate from the subgroup

-Empty cells (.) indicate not enough observation/study to run subgroup analysis.

Table 66. Expanded network estimates of different doses of Ketamine for incidence of GI adverse events

High dose Ketamine	Medium dose Ketamine	Low dose Ketamine	Gabapentin	Ketamine+Midazolam	Ketamine+Magnesium	Ketamine+Methadone	Ketamine+Opioid	Lidocaine	Methadone	Opioid	Placebo
0.19 (0.01,4.46)	1.65 (0.62,4.39)	5.00 (0.26,98.00)	0.19 (0.01,6.25)	1.07 (0.11,10.05)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.31 (0.01,7.88)	1.65 (0.62,4.39)	5.00 (0.26,98.00)	0.19 (0.01,6.25)	1.07 (0.11,10.05)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
1.55 (0.02,125.68)	8.24 (0.36,189.05)	5.00 (0.26,98.00)	0.19 (0.01,6.25)	1.07 (0.11,10.05)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.30 (0.01,9.66)	1.60 (0.30,8.41)	0.97 (0.16,5.81)	0.19 (0.01,6.25)	1.07 (0.11,10.05)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.32 (0.01,10.68)	1.71 (0.32,8.98)	1.03 (0.26,4.18)	0.21 (0.01,5.54)	1.07 (0.11,10.05)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.12 (0.00,5.83)	0.65 (0.06,6.69)	0.39 (0.05,3.27)	0.08 (0.00,3.03)	0.41 (0.03,6.50)	0.38 (0.03,4.81)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.08 (0.00,2.07)	0.44 (0.15,1.23)	0.26 (0.09,0.81)	0.05 (0.00,1.27)	0.27 (0.05,1.62)	0.26 (0.04,1.48)	0.67 (0.06,7.36)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.28 (0.01,7.75)	1.50 (0.54,4.15)	0.91 (0.24,3.49)	0.18 (0.01,4.76)	0.94 (0.14,6.47)	0.88 (0.13,5.85)	2.30 (0.19,28.29)	3.42 (0.82,14.20)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.09 (0.00,4.19)	0.49 (0.05,4.68)	0.30 (0.04,2.27)	0.06 (0.00,2.18)	0.30 (0.02,4.60)	0.29 (0.02,3.38)	0.75 (0.21,2.71)	1.12 (0.11,11.40)	0.33 (0.03,3.75)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
0.12 (0.01,2.69)	0.64 (0.35,1.17)	0.39 (0.16,0.96)	0.08 (0.00,1.74)	0.40 (0.09,1.88)	0.37 (0.07,1.90)	0.98 (0.10,9.82)	1.46 (0.61,3.51)	0.43 (0.13,1.36)	1.31 (0.14,12.20)	8.97 (3.85,20.94)	
1.08 (0.04,27.01)	5.73 (2.37,13.87)	3.48 (1.73,7.00)	0.70 (0.03,14.79)	3.59 (0.62,20.95)	3.36 (0.76,14.90)	8.83 (0.95,81.99)	13.13 (4.33,39.80)	3.83 (1.09,13.53)	11.77 (1.36,101.63)	8.97 (3.85,20.94)	

Table 67. Expanded network estimates of different delivery methods of Ketamine for incidence of GI adverse events

IV Ketamine	Transderamal Ketamine	Clonidine	Fentanyl+Ketamine	Ketamine+Clonidine	Ketamine+Midazolan	Ketamine+Magnesium	Ketamine+Opioid	Lidocaine	Opioid	Placebo
1.15 (0.11,11.70)	0.55 (0.02,17.85)	0.27 (0.01,5.70)	3.38 (0.16,71.67)	2.38 (0.07,85.11)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
0.63 (0.02,16.43)	0.55 (0.02,17.85)	0.27 (0.01,5.70)	3.38 (0.16,71.67)	2.38 (0.07,85.11)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
0.17 (0.02,1.72)	0.15 (0.01,2.02)	0.27 (0.01,5.70)	3.38 (0.16,71.67)	2.38 (0.07,85.11)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
0.57 (0.02,14.69)	0.50 (0.02,15.97)	0.90 (0.02,40.84)	3.38 (0.16,71.67)	2.38 (0.07,85.11)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
1.36 (0.26,6.97)	1.18 (0.07,19.11)	2.14 (0.06,77.06)	8.03 (0.51,126.94)	2.38 (0.07,85.11)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
1.07 (0.26,4.31)	0.93 (0.06,13.63)	1.69 (0.05,57.80)	6.32 (0.43,93.82)	1.87 (0.06,63.83)	0.79 (0.09,6.73)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
0.37 (0.14,0.93)	0.32 (0.03,3.44)	0.58 (0.02,14.87)	2.17 (0.22,21.80)	0.64 (0.03,16.42)	0.27 (0.05,1.57)	0.34 (0.06,1.82)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
1.42 (0.51,3.92)	1.23 (0.10,15.28)	2.24 (0.07,67.39)	8.39 (0.67,104.85)	2.49 (0.08,74.41)	1.04 (0.15,7.15)	1.33 (0.24,7.40)	3.87 (0.98,15.25)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
0.54 (0.32,0.93)	0.47 (0.05,4.78)	0.86 (0.03,21.69)	3.21 (0.33,31.60)	0.95 (0.04,23.95)	0.40 (0.09,1.88)	0.51 (0.11,2.25)	1.48 (0.64,3.43)	0.38 (0.12,1.20)	7.38 (3.50,15.54)	
4.00 (2.18,7.35)	3.48 (0.35,34.78)	6.32 (0.24,167.55)	23.70 (2.26,248.63)	7.02 (0.27,184.96)	2.95 (0.53,16.43)	3.75 (0.87,16.21)	10.93 (3.81,31.33)	2.83 (0.91,8.81)	7.38 (3.50,15.54)	

Table 68. Expanded network estimates of different doses of Ketamine for incidence of dizziness

High dose Ketamine	Medium dose Ketamine	Low dose Ketamine	Ketamine+Midazolam	Ketamine+Magnesium	Ketamine+Methadone	Lidocaine	Methadone	Opioid	Placebo
0.99 (0.05,19.57)	**3.77 (1.41,10.10)**								
3.75 (0.18,79.44)	2.86 (1.12,7.26)	0.76 (0.39,1.49)							
2.84 (0.13,60.19)	1.17 (0.11,12.80)	0.31 (0.03,3.21)	0.41 (0.04,4.45)						
1.16 (0.03,44.90)	22.01 (0.99,487.33)	5.83 (0.31,109.99)	7.70 (0.38,156.84)	18.82 (0.44,802.68)					
21.85 (0.32,1512.34)	1.76 (0.48,6.39)	0.47 (0.10,2.08)	0.62 (0.14,2.64)	1.50 (0.10,21.65)	0.08 (0.00,2.16)				
1.75 (0.07,43.87)	7.34 (0.89,60.80)	1.94 (0.30,12.64)	2.57 (0.35,18.78)	6.27 (0.31,125.24)	0.33 (0.01,7.50)	4.17 (0.38,45.77)			
7.28 (0.20,261.85)	3.03 (1.29,7.09)	0.80 (0.46,1.40)	1.06 (0.72,1.55)	2.59 (0.25,27.27)	0.14 (0.01,2.73)	1.72 (0.42,7.01)	0.41 (0.06,2.91)		
3.00 (0.14,62.24)	9.07 (3.35,24.53)	2.40 (0.73,7.95)	3.17 (0.96,10.52)	7.75 (0.75,80.22)	0.41 (0.02,9.82)	5.15 (1.06,25.01)	1.24 (0.13,11.40)	3.00 (0.96,9.34)	
9.00 (0.54,149.50)									

Table 69. Expanded network estimates of different delivery methods of Ketamine for incidence of dizziness

IV Ketamine	Transdermal Ketamine	Ketamine+Midazolam	Ketamine+Magnesium	Lidocaine	Opioid	Placebo
37.18 (2.51,551.09)						
1.55 (0.30,7.93)	0.04 (0.00,0.94)					
0.50 (0.04,6.47)	0.01 (0.00,0.48)	0.32 (0.02,6.62)				
1.48 (0.32,6.83)	0.04 (0.00,0.85)	0.95 (0.11,7.93)	2.97 (0.15,57.70)			
1.64 (0.63,4.26)	0.04 (0.00,0.74)	1.06 (0.28,3.98)	3.29 (0.22,49.92)	1.11 (0.21,5.79)		
6.20 (2.22,17.33)	0.17 (0.01,2.01)	4.00 (0.61,26.20)	12.45 (0.96,161.77)	4.20 (0.71,24.95)	3.78 (1.00,14.32)	

Table 70. Expanded network estimates of different doses of Ketamine for incidence of fatigue, somnolence, and sedation

Medium dose Ketamine	Low dose Ketamine	Ketamine+Midazolam	Ketamine+Magnesium	Ketamine+Methadone	Ketamine+Opioid	Lidocaine	Methadone	Opioid	Placebo
0.83 (0.51,1.33)									
0.54 (0.29,0.97)	0.65 (0.39,1.09)								
1.67 (0.45,6.17)	2.02 (0.57,7.13)	3.12 (0.81,11.98)							
0.33 (0.08,1.41)	0.39 (0.10,1.57)	0.61 (0.14,2.66)	0.20 (0.03,1.27)						
0.65 (0.42,1.01)	0.79 (0.61,1.02)	1.22 (0.76,1.95)	0.39 (0.11,1.40)	2.00 (0.49,8.19)					
1.36 (1.01,1.82)	1.64 (0.97,2.78)	2.53 (1.34,4.79)	0.81 (0.22,3.07)	4.17 (0.95,18.32)	2.08 (1.28,3.39)				
0.16 (0.04,0.63)	0.20 (0.06,0.70)	0.30 (0.08,1.19)	0.10 (0.02,0.58)	0.50 (0.27,0.92)	0.25 (0.07,0.91)	0.12 (0.03,0.47)			
0.69 (0.46,1.03)	0.83 (0.63,1.09)	1.29 (0.83,1.99)	0.41 (0.12,1.47)	2.12 (0.52,8.67)	1.06 (0.89,1.26)	0.51 (0.32,0.81)	4.23 (1.16,15.41)		
3.00 (1.78,5.07)	3.64 (2.09,6.32)	5.61 (2.84,11.09)	1.80 (0.50,6.49)	9.23 (2.08,40.99)	4.61 (2.71,7.84)	2.22 (1.24,3.94)	18.46 (4.65,73.33)	4.36 (2.59,7.35)	

Table 71. Expanded network estimates of different delivery methods of Ketamine for incidence of fatigue, somnolence, and sedation

IV Ketamine	Transdermal	Ketamine+Midazolam	Ketamine+Magnesium	Ketamine+Opioid	Lidocaine	Opioid	Placebo
1.98 (0.22,17.78)							
0.62 (0.38,1.02)	0.31 (0.03,2.94)						
1.86 (0.53,6.52)	0.94 (0.08,11.32)	2.99 (0.78,11.48)					
0.76 (0.60,0.96)	0.38 (0.04,3.46)	1.23 (0.77,1.96)	0.41 (0.11,1.46)				
1.38 (1.03,1.85)	0.69 (0.08,6.32)	2.22 (1.26,3.90)	0.74 (0.20,2.68)	1.81 (1.26,2.60)			
0.80 (0.63,1.00)	0.40 (0.04,3.62)	1.29 (0.83,1.99)	0.43 (0.12,1.53)	1.05 (0.88,1.24)	0.58 (0.41,0.83)		
2.98 (1.88,4.71)	1.50 (0.18,12.80)	4.79 (2.50,9.20)	1.60 (0.45,5.70)	3.91 (2.41,6.34)	2.16 (1.27,3.69)	3.73 (2.30,6.04)	

Table 72. Expanded network estimates of different doses of Ketamine for incidence of dissociative symptoms

High dose Ketamine											
1.14 (0.05,23.91)	**Medium dose Ketamine**										
3.17 (0.17,59.64)	2.77 (0.90,8.49)	**Low dose Ketamine**									
0.09 (0.00,5.28)	0.08 (0.00,1.64)	0.03 (0.00,0.48)	**Gabapentin**								
2.56 (0.12,56.62)	2.24 (0.61,8.23)	0.81 (0.26,2.49)	28.30 (1.37,586.11)	**Ketamine+Midazolam**							
4.97 (0.15,166.06)	4.34 (0.46,40.77)	1.57 (0.22,11.21)	54.87 (1.77,1699.56)	1.94 (0.20,18.46)	**Ketamine+Magnesium**						
11.10 (0.15,832.27)	9.69 (0.34,278.89)	3.50 (0.15,83.08)	122.49 (1.77,8471.18)	4.33 (0.15,124.74)	2.23 (0.05,92.87)	**Ketamine+Methadone**					
2.60 (0.10,68.24)	2.27 (0.41,12.63)	0.82 (0.18,3.80)	28.73 (1.17,707.93)	1.02 (0.21,4.98)	0.52 (0.04,6.27)	0.23 (0.01,7.91)	**Ketamine+Opioid**				
2.82 (0.12,64.53)	2.47 (1.10,5.54)	0.89 (0.23,3.39)	31.17 (1.38,702.04)	1.10 (0.24,5.01)	0.57 (0.05,6.00)	0.25 (0.01,7.91)	1.08 (0.17,7.11)	**Lidocaine**			
11.10 (0.15,832.27)	9.69 (0.34,278.89)	3.50 (0.15,83.08)	122.49 (1.77,8471.18)	4.33 (0.15,124.74)	2.23 (0.05,92.87)	1.00 (0.02,49.32)	4.26 (0.13,143.85)	3.93 (0.13,122.20)	**Methadone**		
5.34 (0.27,107.63)	4.67 (1.61,13.53)	1.68 (0.73,3.91)	58.96 (3.13,1111.91)	2.08 (0.99,4.40)	1.07 (0.13,9.01)	0.48 (0.02,12.75)	2.05 (0.50,8.36)	1.89 (0.51,7.07)	0.48 (0.02,12.75)	**Opioid**	
11.00 (0.64,190.14)	9.61 (3.34,27.62)	3.47 (1.72,6.99)	121.43 (6.69,2205.65)	4.29 (1.28,14.34)	2.21 (0.29,17.14)	0.99 (0.04,25.40)	4.23 (0.86,20.86)	3.90 (1.07,14.18)	0.99 (0.04,25.40)	2.06 (0.80,5.31)	**Placebo**

Table 73. Expanded network estimates of different delivery methods of Ketamine for incidence of dissociative symptoms

IV-Ketamine							
9.50 (0.54,168.59)	**Transdermal Ketamine**						
1.14 (0.34,3.81)	0.12 (0.01,2.66)	**Ketamine+Midazolam**					
1.65 (0.22,12.50)	0.17 (0.01,5.72)	1.45 (0.14,15.27)	**Ketamine+Magnesium**				
1.08 (0.23,5.06)	0.11 (0.00,2.91)	0.95 (0.17,5.21)	0.65 (0.05,8.29)	**Ketamine+Opioid**			
2.40 (1.01,5.69)	0.25 (0.01,5.02)	2.11 (0.48,9.21)	1.45 (0.16,13.08)	2.23 (0.38,13.04)	**Lidocaine**		
2.37 (1.07,5.26)	0.25 (0.01,4.85)	2.08 (0.84,5.16)	1.43 (0.16,12.58)	2.20 (0.52,9.33)	0.99 (0.31,3.15)	**Opioid**	
4.75 (2.40,9.41)	0.50 (0.03,8.17)	4.18 (1.08,16.09)	2.88 (0.35,23.43)	4.41 (0.84,23.07)	1.98 (0.68,5.71)	2.00 (0.74,5.43)	**Placebo**

Table 74. Expanded network estimates of different doses of Ketamine for incidence of visual impairment

Medium dose Ketamine	Low dose Ketamine	Gabapentin	Ketamine+Midazolam	Lidocaine	Opioid	Placebo
0.80 (0.08,8.54)						
0.27 (0.01,13.67)	0.33 (0.01,7.72)					
1.01 (0.22,4.62)	1.26 (0.11,14.16)	3.79 (0.07,199.62)				
5.88 (1.48,23.36)	7.31 (0.48,111.11)	21.92 (0.34,1401.15)	5.79 (0.75,44.65)			
3.25 (0.92,11.44)	4.04 (0.42,38.90)	12.12 (0.25,583.27)	3.20 (1.38,7.44)	0.55 (0.09,3.55)		
9.76 (2.50,38.11)	12.13 (1.26,116.89)	36.40 (0.76,1752.47)	9.61 (1.58,58.41)	1.66 (0.25,11.17)	3.00 (0.61,14.80)	

Table 75. Network estimates for incidence of GI adverse events by excluding stand-alone nodes

Ketamine	Ketamine+Magnesium	Ketamine+Methadone	Ketamine+Opioid	Lidocaine	Methadone	Opioid	Placebo
1.07 (0.26,4.30)							
0.39 (0.05,3.27)	0.37 (0.03,4.66)						
0.34 (0.13,0.89)	0.32 (0.06,1.72)	0.87 (0.09,8.83)					
1.42 (0.51,3.91)	1.33 (0.24,7.40)	3.59 (0.34,37.58)	4.14 (1.03,16.60)				
0.30 (0.04,2.27)	0.28 (0.02,3.28)	0.75 (0.21,2.71)	0.87 (0.09,8.21)	0.21 (0.02,2.04)			
0.53 (0.31,0.91)	0.50 (0.11,2.21)	1.35 (0.15,11.99)	1.56 (0.66,3.69)	0.38 (0.12,1.18)	1.80 (0.22,14.83)		
3.97 (2.18,7.22)	3.72 (0.86,16.06)	10.07 (1.12,90.80)	11.61 (3.95,34.11)	2.80 (0.90,8.71)	13.43 (1.60,112.42)	7.45 (3.53,15.73)	

Table 76. Network estimates for incidence of dizziness by excluding stand-alone nodes

Ketamine						
0.38 (0.02,6.75)	Ketamine+Magnesium					
5.83 (0.17,198.06)	15.25 (0.16,1437.98)	Ketamine+Methadone				
1.40 (0.23,8.51)	3.65 (0.13,105.44)	0.24 (0.00,12.58)	Lidocaine			
1.94 (0.13,29.00)	5.08 (0.10,262.18)	0.33 (0.01,13.13)	1.39 (0.05,35.91)	Methadone		
1.60 (0.47,5.46)	4.19 (0.19,92.00)	0.27 (0.01,11.47)	1.15 (0.16,8.26)	0.82 (0.04,16.03)	Opioid	
3.66 (1.25,10.74)	9.56 (0.54,168.86)	0.63 (0.02,25.00)	2.62 (0.35,19.43)	1.88 (0.10,34.50)	2.28 (0.51,10.23)	Placebo

Table 77. Network estimates for incidence of fatigue, somnolence, and sedation by excluding stand-alone nodes

Ketamine							
1.84 (0.52,6.44)	Ketamine+Magnesium						
0.39 (0.10,1.57)	0.21 (0.03,1.39)	Ketamine+Methadone					
0.76 (0.60,0.96)	0.41 (0.12,1.48)	1.93 (0.47,7.85)	Ketamine+Opioid				
1.38 (1.03,1.84)	0.75 (0.21,2.71)	3.49 (0.85,14.37)	1.81 (1.26,2.60)	Lidocaine			
0.20 (0.06,0.70)	0.11 (0.02,0.64)	0.50 (0.27,0.92)	0.26 (0.07,0.94)	0.14 (0.04,0.52)	Methadone		
0.80 (0.63,1.00)	0.43 (0.12,1.55)	2.02 (0.50,8.23)	1.05 (0.88,1.24)	0.58 (0.41,0.83)	4.05 (1.12,14.61)	Opioid	
2.89 (1.84,4.53)	1.57 (0.44,5.59)	7.33 (1.71,31.42)	3.80 (2.36,6.12)	2.10 (1.24,3.55)	14.66 (3.84,56.05)	3.62 (2.26,5.82)	Placebo

Table 78. Network estimates for incidence of dissociative symptoms by excluding stand-alone nodes

Ketamine							
1.62 (0.21,12.29)	Ketamine+Magnesium						
3.50 (0.14,86.89)	2.16 (0.05,96.58)	Ketamine+Methadone					
1.06 (0.22,5.00)	0.65 (0.05,8.38)	0.30 (0.01,10.71)	Ketamine+Opioid				
2.39 (1.00,5.68)	1.48 (0.16,13.36)	0.68 (0.02,18.99)	2.25 (0.38,13.25)	Lidocaine			
3.50 (0.14,86.89)	2.16 (0.05,96.58)	1.00 (0.02,51.16)	3.31 (0.09,117.03)	1.47 (0.05,40.83)	Methadone		
2.34 (1.05,5.22)	1.45 (0.16,12.78)	0.67 (0.02,18.34)	2.21 (0.52,9.41)	0.98 (0.31,3.15)	0.67 (0.02,18.34)	Opioid	
4.22 (2.20,8.10)	2.61 (0.32,21.21)	1.21 (0.05,31.97)	3.99 (0.77,20.72)	1.77 (0.62,5.07)	1.21 (0.05,31.97)	1.80 (0.67,4.83)	Placebo

Table 79. Network estimates for incidence of visual impairment by excluding stand-alone nodes

Ketamine			
5.89 (1.48,23.39)	Lidocaine		
3.38 (1.03,11.03)	0.57 (0.09,3.52)	Opioid	
10.21 (2.86,36.42)	1.73 (0.27,11.00)	3.02 (0.61,14.86)	Placebo