# Subanesthetic Ketamine in Serious Illness

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https://vetpol.co.uk/blogs/jeremy/34478-special-k-ketamine-is-a-special-drug-that-s-why-we-need-to-keep-it-and-look-after-it

# Disclosures

- No disclosures for ineligible companies
- FDA approved use and off-label use of ketamine will be discussed

# Objectives

1. Briefly review history of ketamine
2. Understand unique pharmacology of ketamine
3. Review evidence for its use in treating pain and mood disorders
4. Appreciate safety and toxicity concerns
5. Identify appropriate patient candidates
6. Formulate dosing strategies

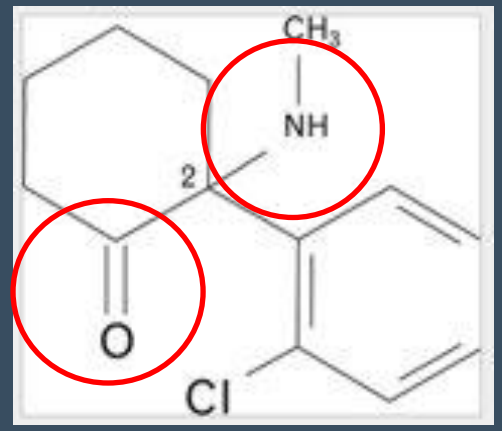
# Why Ketamine?

“Serious illness” is a health condition that carries a high risk of mortality AND either negatively impacts a person's daily function or quality of life, OR excessively strains their caregivers.

- High burden of mental distress and pain refractory to multimodal care or with limited prognosis

Kelley AS, Bollens-Lund E. Identifying the Population with Serious Illness: The "Denominator" Challenge. *J Palliat Med*. 2018;21(S2):S7-S16.

# History




1956 – synthesis of phencyclidine (PCP)

1962 – synthesis of CI-5181

1960s – first reports of recreational use. Significant use in field in Vietnam war

1970 – FDA approval of racemic Ketalar for induction and maintenance of GA

1980s – Discovery of N-methyl-D-aspartate receptor (NMDAR)

2000 – Discovery of rapid and powerful antidepressant effect by Yale researchers

2019 – FDA approval of intranasal esketamine (Spravato) as combination therapy in TRD

2020 – FDA approval of intranasal esketamine expanded to include MDD and suicidal ideation

2025 – FDA approval of  intranasal esketamine as monotherapy for TRD

Mion G. History of anaesthesia: The ketamine story - past, present and future. *Eur J Anaesthesiol*. 2017;34(9):571-575.

Nowacka A, Borczyk M. Ketamine applications beyond anesthesia - A literature review. *Eur J Pharmacol*. 2019;860:172547.

Subramanian S, Haroutounian S, Palanca BJA, Lenze EJ. Ketamine as a therapeutic agent for depression and pain: mechanisms and evidence. *J Neurol Sci*. 2022;434:120152.

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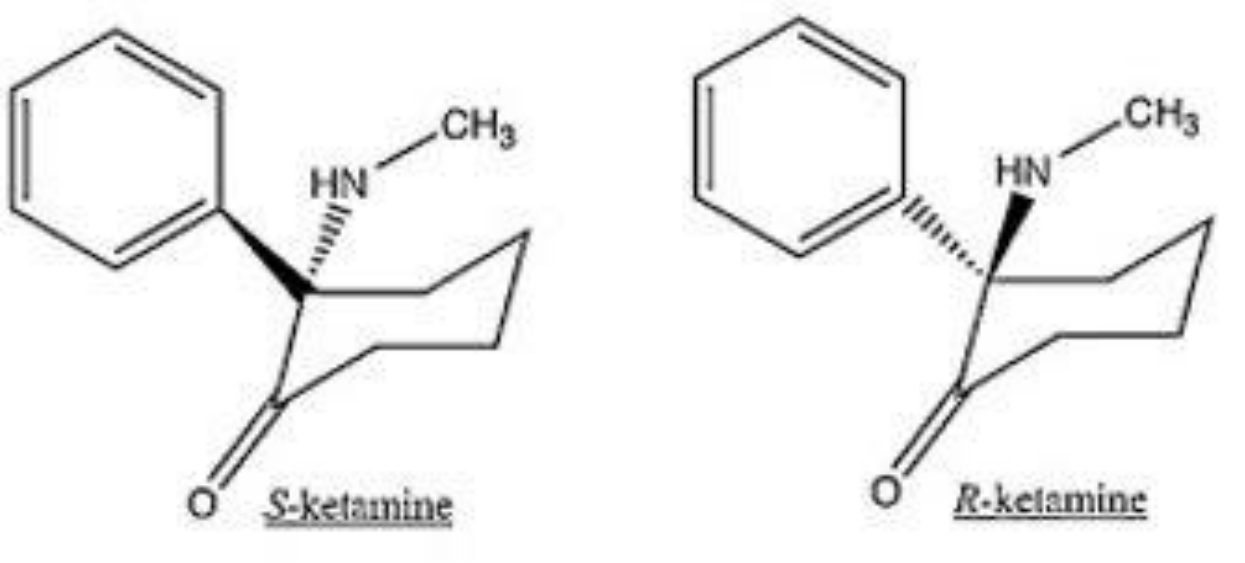
# Pharmacology



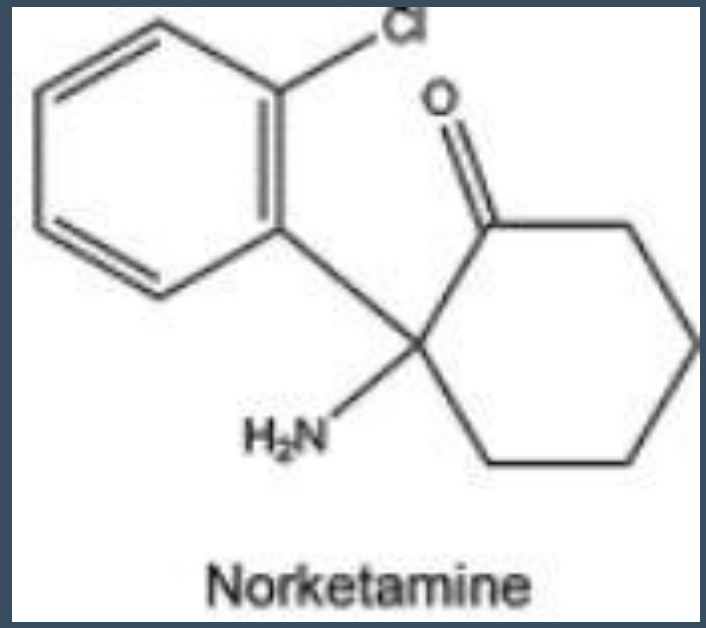

| Formulation | Bioavailability |
|---|---|
| Intravenous | 100% |
| Intramuscular | 95% |
| Intranasal | 50% |
| Sublingual | 30% |
| Rectal | 30% |
| Oral | 17% |

Porpiglia N, Musile G, Bortolotti F, De Palo EF, Tagliaro F. Chiral separation and determination of ketamine and norketamine in hair by capillary electrophoresis. *Forensic Sci Int*. 2016;266:304-310.

PMID: 35092901.

# Pharmacokinetics

- ~30% plasma protein binding ability
- Oxidation via CYP450
  - CYP2B6
  - CYP3A4




- Norketamine is primary metabolite
  - Hydroxynorketamine secondary metabolite
- Primarily renally excreted but given short half life dosing adjustments not necessary in renal impairment

# Pharmacokinetics

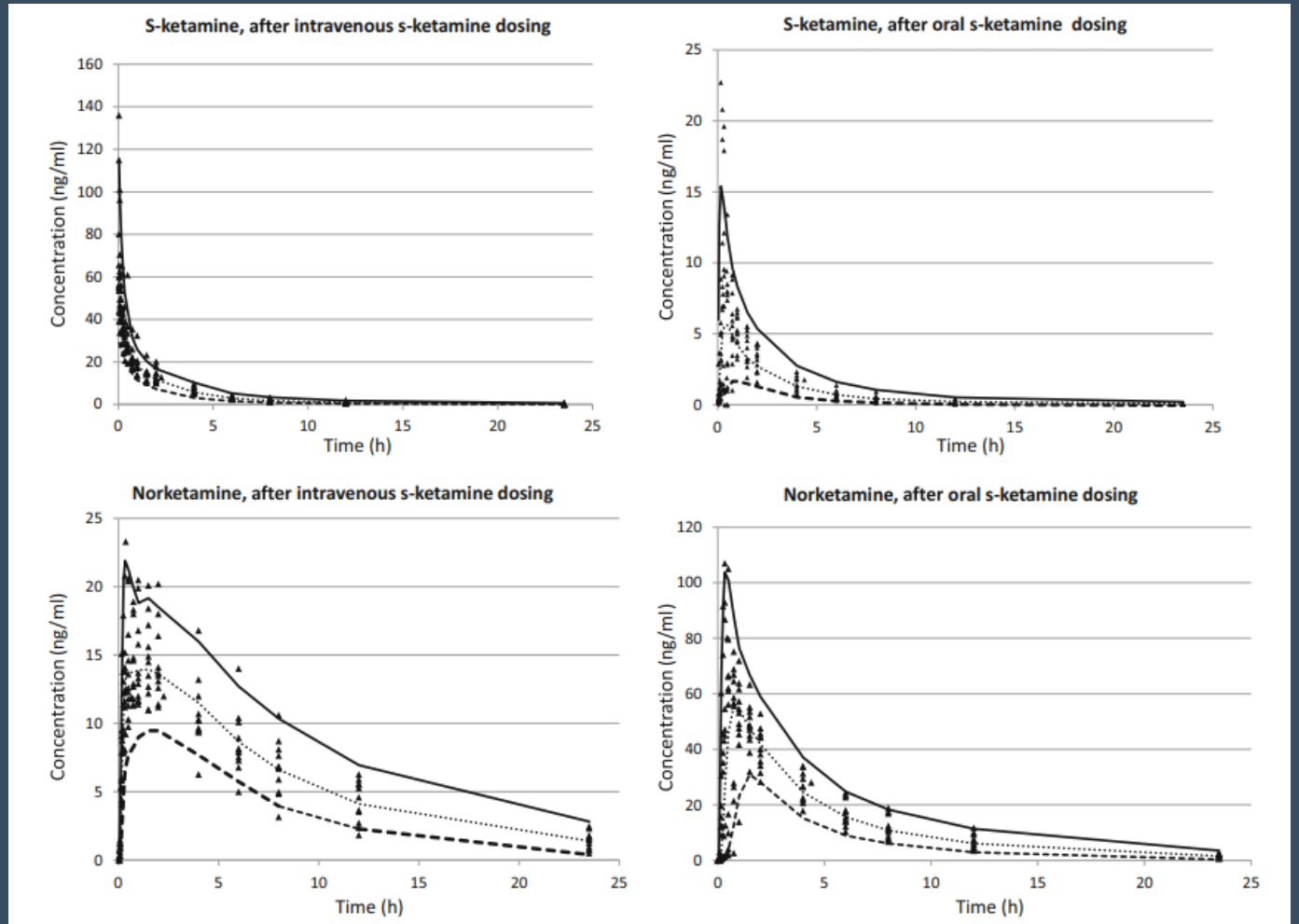
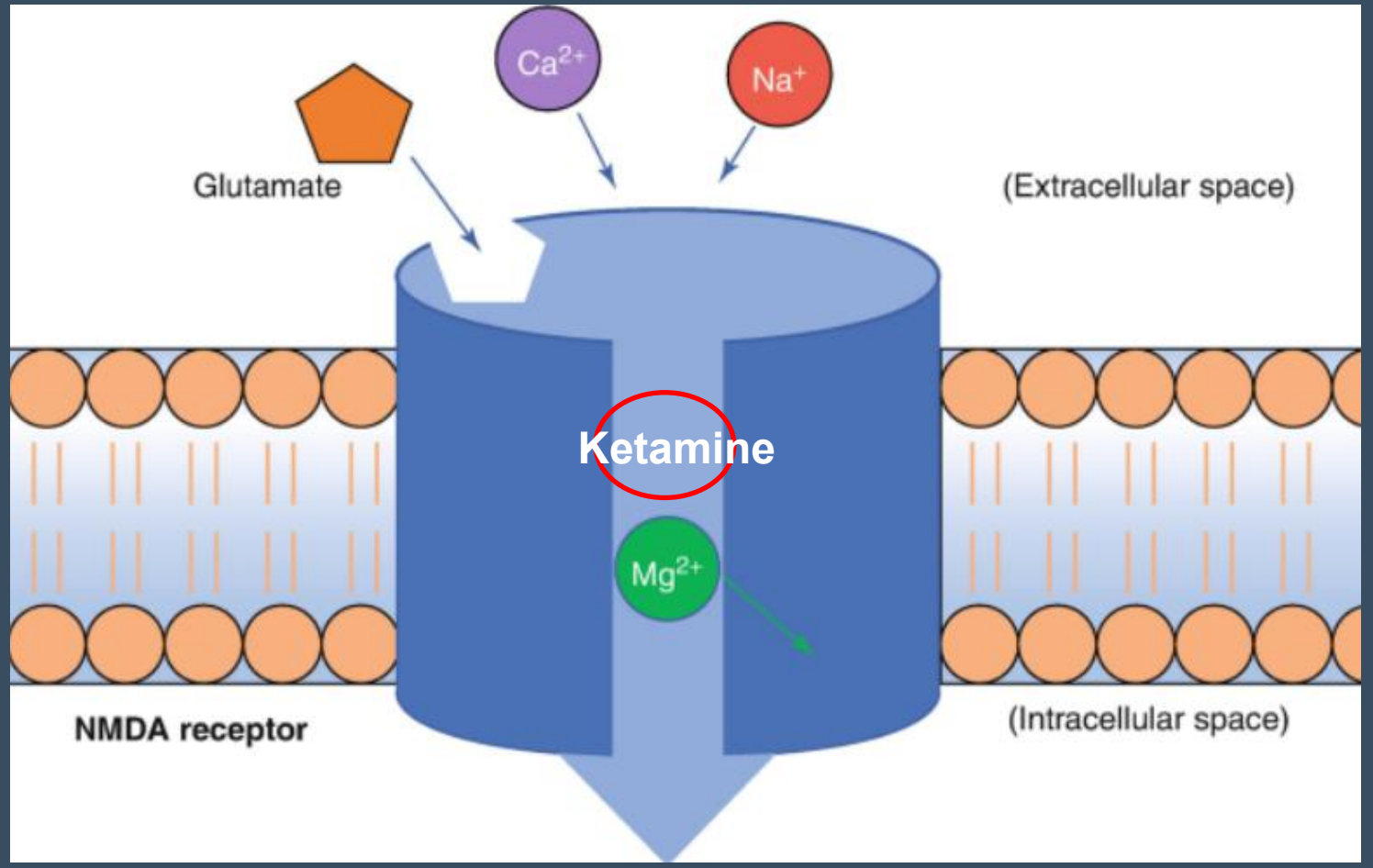



**Fig. 2** Visual predictive check for model validation of *S*-ketamine and norketamine pharmacokinetics in 11 healthy male volunteers. The *dashed middle lines* depict the median of the simulated data, the *lower dotted lines* indicate the lower 5th percentile of the simulated concentrations, and the *upper uninterrupted lines* indicate the 95th percentile of the simulated concentrations. The *triangles* are the observed concentration data

PMID: 25724645.

# Mechanism of action - Pain




PMID: 35092901.
https://doi.org/10.1007/978-3-030-12281-2_24

# Wind up Phenomenon

Dad?

Dad?

Dad?

Dad?

Dad?

Dad?

Dad?

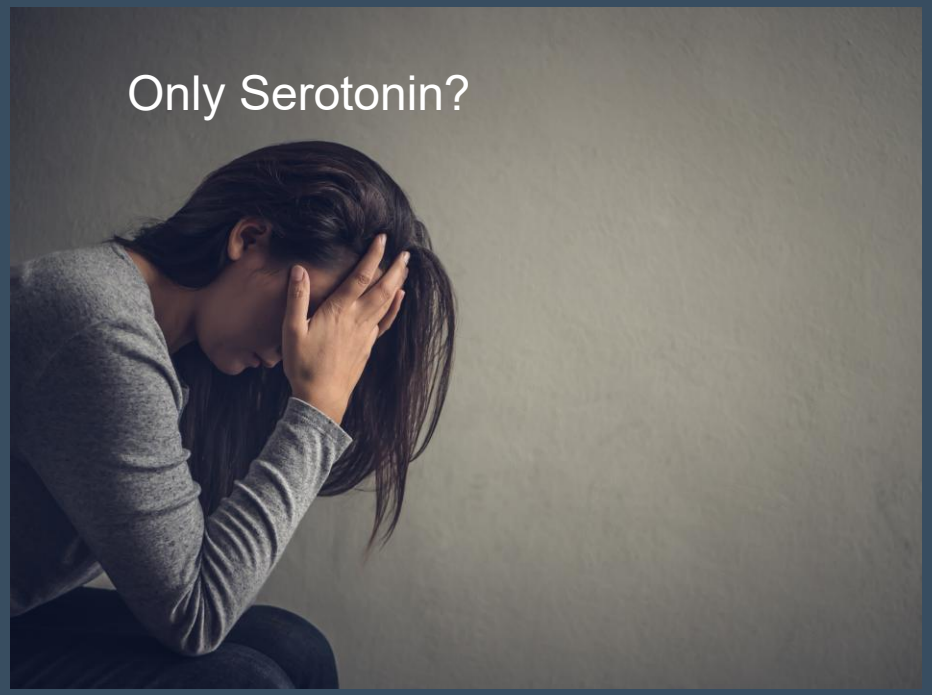
# Mechanism of Action

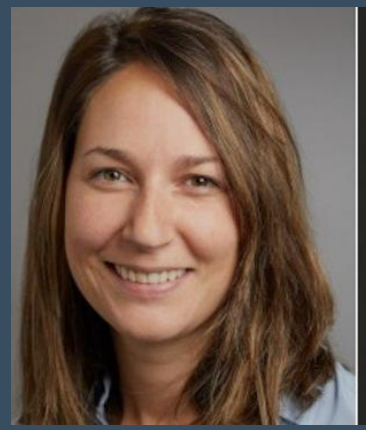
Additional areas of involvement:

1. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)
2. Hyperpolarization-activated cyclic nucleotide-gated channels (HCN)
3. Opioid receptors
4. Monoaminergic pathways
5. Inflammatory pathways

PMID: 35092901.

# Mechanism of Action - Depression



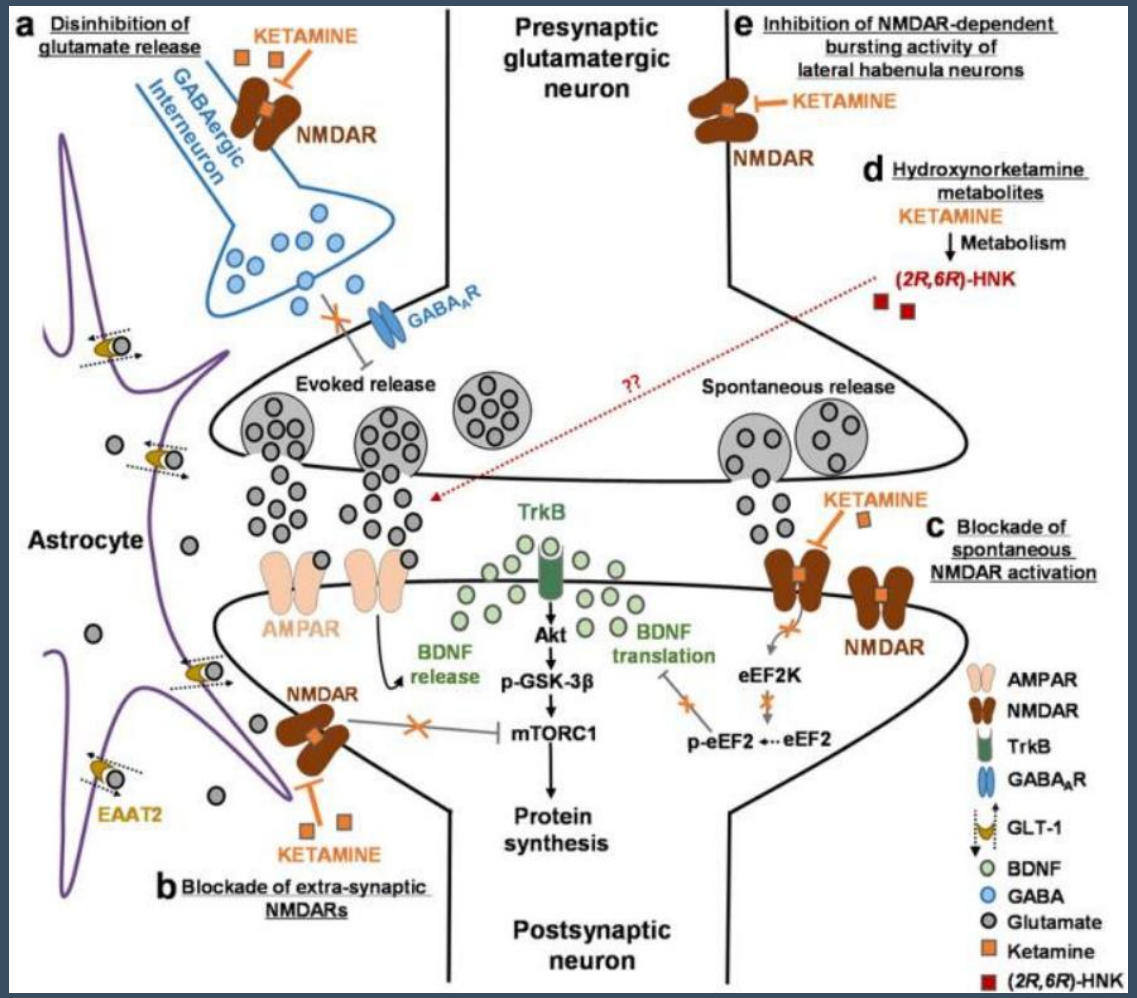
https://www.rockefeller.edu/news/27135-neuroscientist-bruce-mcewen-studied-impact-stress-brain-died/

https://i1.rgstatic.net/ii/profile.image/272917053308928-1442079904048_Q512/Pedro-Delgado-10.jpg

https://tim.blog/2022/10/03/dr-john-krystal-ketamine-transcript/

https://pbs.twimg.com/media/D3UL34JXkAUP_2r.jpg

# Mechanism of Action - Depression




1. Ketamine antagonizes NMDARs on GABA interneurons
2. Those interneurons momentarily inhibit less
3. These disinhibited pyramidal cells fire more and extra glutamate is released into synapses
4. Glutamate preferentially drives AMPA receptors on post synaptic neurons
5. AMPA throughput (and MOR agonism) triggers BDNF release, leading mTOR to regrow and stabilize synaptic connections

doi:10.1038/mp.2017.255

doi:10.1176/appi.ajp.20240378

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# Physiologic effects of ketamine

**Table 1.** Physiologic effects of ketamine

| Organ system | Effect |
|---|---|
| Cardiovascular | ↑ Heart rate/CO |
| | ↑ Myocardial work |
| Neurologic | ↓ Excitatory neurotransmitters |
| | ↑ Cerebral oxygen consumption |
| | ↑ Cerebral perfusion |
| | ↑ Intracranial pressure |
| Respiratory | Bronchodilation |
| Miscellaneous | ↑ Intraocular pressure |
| | Hypersalivation |

Absolute Contraindications:
1. History of allergy to ketamine
2. History of schizophrenia

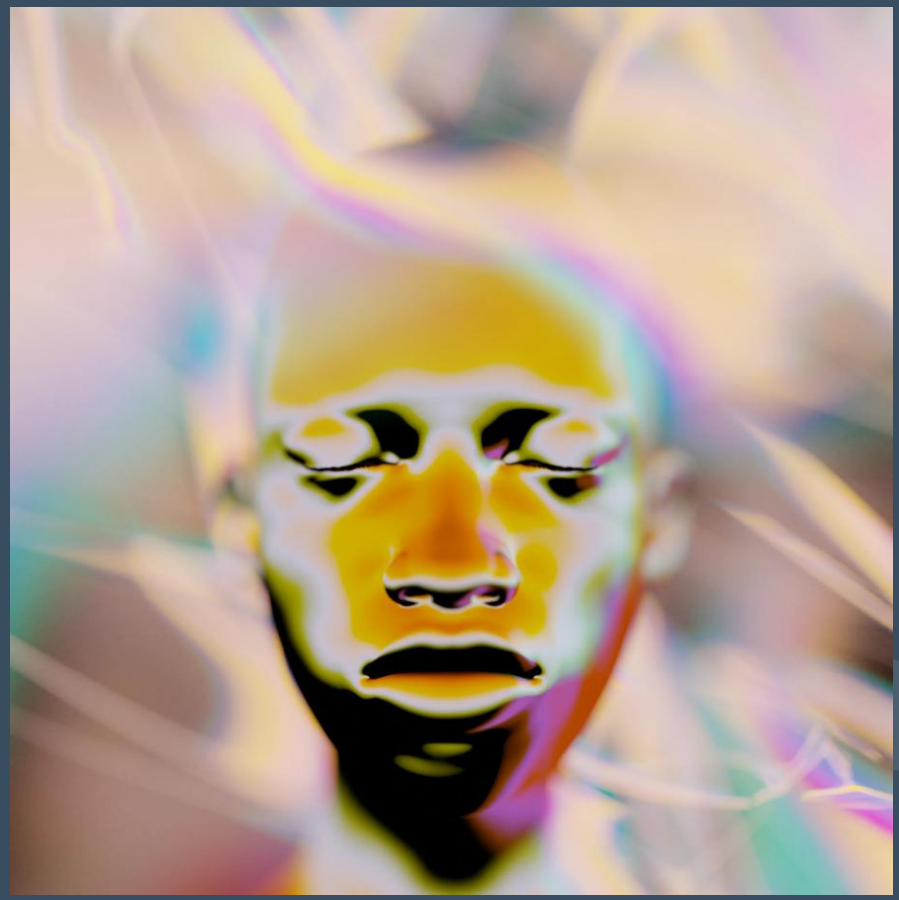
Relative Contraindications
1. Substance use disorder
2. Cardiovascular conditions
3. Chronic liver disease

PMID: 32826629.

https://www.ncbi.nlm.nih.gov/books/NBK470357/

# Safety

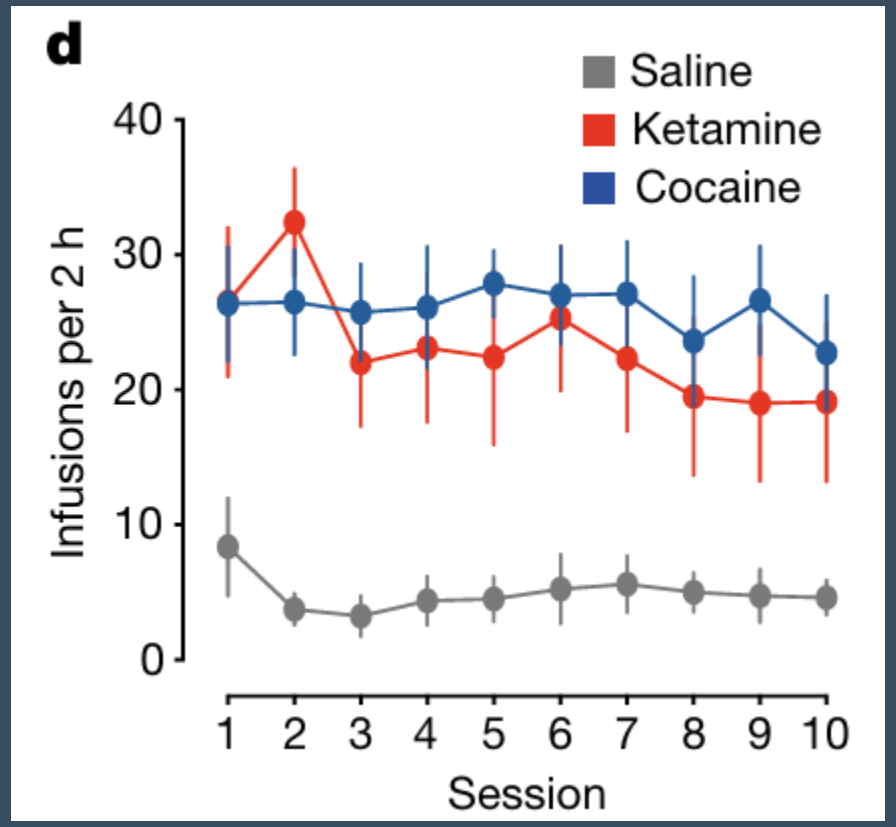
- Drug interactions (CYP3A4):
  - clarithromycin and grapefruit juice
  - Rifampin and St. John's wort
- Psychomimetic phenomena
- Urinary tract toxicity
- Hepatobiliary toxicity
- Cardiovascular

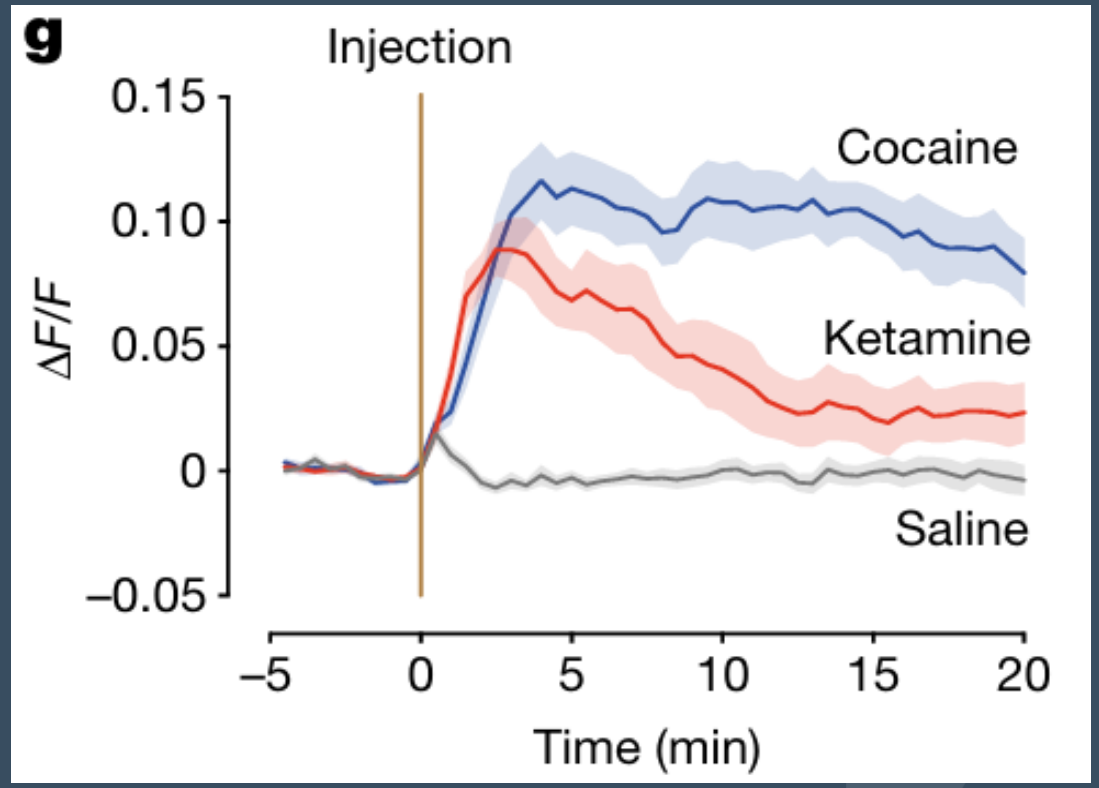


PMID: 26096492.

https://media.newyorker.com/photos/61c36010a781a26a4a73ffb5/1:1/w_2560,h_2560,c_limit/Witt_Ketamine.png

# Misuse / Addiction risk




PMID: 35896744.

# Cognitive Impairment

- Preclinical studies suggest neurotoxic effects
  - Doses exceed clinical or recreational doses
- Acute IV subanesthetic doses have been shown to impact memory, semantic processing and procedural learning
  - Effects resolved within 3 days
- Chronic recreational use shows similar acute effects on memory
  - Cessation of use for one year led to an improvement in memory performance

PMID: 38518272

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# Indications

- FDA approved: Induction and maintenance of general anesthesia; Treatment-resistant depression (esketamine) as monotherapy; Suicidal ideation with MDD

- Off label: Acute pain, neuropathic pain, complex regional pain syndrome, opioid induced hyperalgesia, fibromyalgia, suicidal ideation, PTSD, substance use disorder...whatever the social media algorithm suggests?

PMID: 32826629.

# Caution – Heterogeneity ahead

https://static.s4be.cochrane.org/app/uploads/2018/10/rawpixel-532413-unsplash-e1543507896731.jpg

# Acute Perioperative Pain

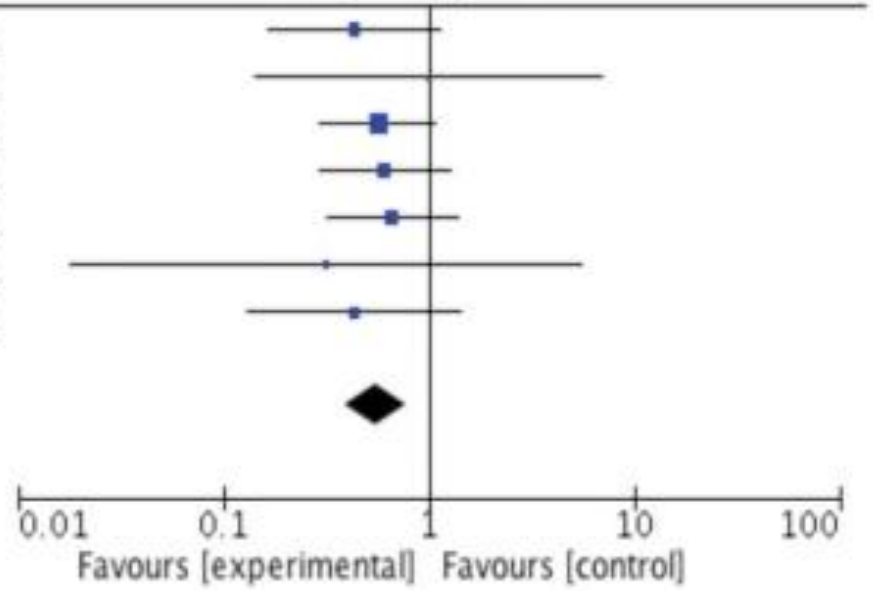
PMID: 27780181.

A

| Study or Subgroup | Ketamine-Opioid PCA Events | Total | Opioid PCA Events | Total | Weight | Risk Ratio M-H, Fixed, 99% CI |
|---|---|---|---|---|---|---|
| Cha 2012 | 7 | 30 | 16 | 30 | 16.6% | 0.44 [0.17, 1.14] |
| Yeom 2012 | 3 | 20 | 3 | 20 | 3.1% | 1.00 [0.14, 6.95] |
| Sami 2008 | 17 | 67 | 30 | 67 | 31.2% | 0.57 [0.30, 1.08] |
| Chazan 2010 | 10 | 24 | 15 | 22 | 16.3% | 0.61 [0.30, 1.26] |
| Nesher 2008 | 11 | 28 | 17 | 29 | 17.4% | 0.67 [0.32, 1.39] |
| Nesher 2009 | 1 | 21 | 3 | 20 | 3.2% | 0.32 [0.02, 5.56] |
| Kollender 2008 | 5 | 28 | 12 | 29 | 12.3% | 0.43 [0.13, 1.42] |
| **Total (98% CI)** | | **218** | | **217** | **100.0%** | **0.56 (0.40, 0.78)** |
| Total events | 54 | | 96 | | | |

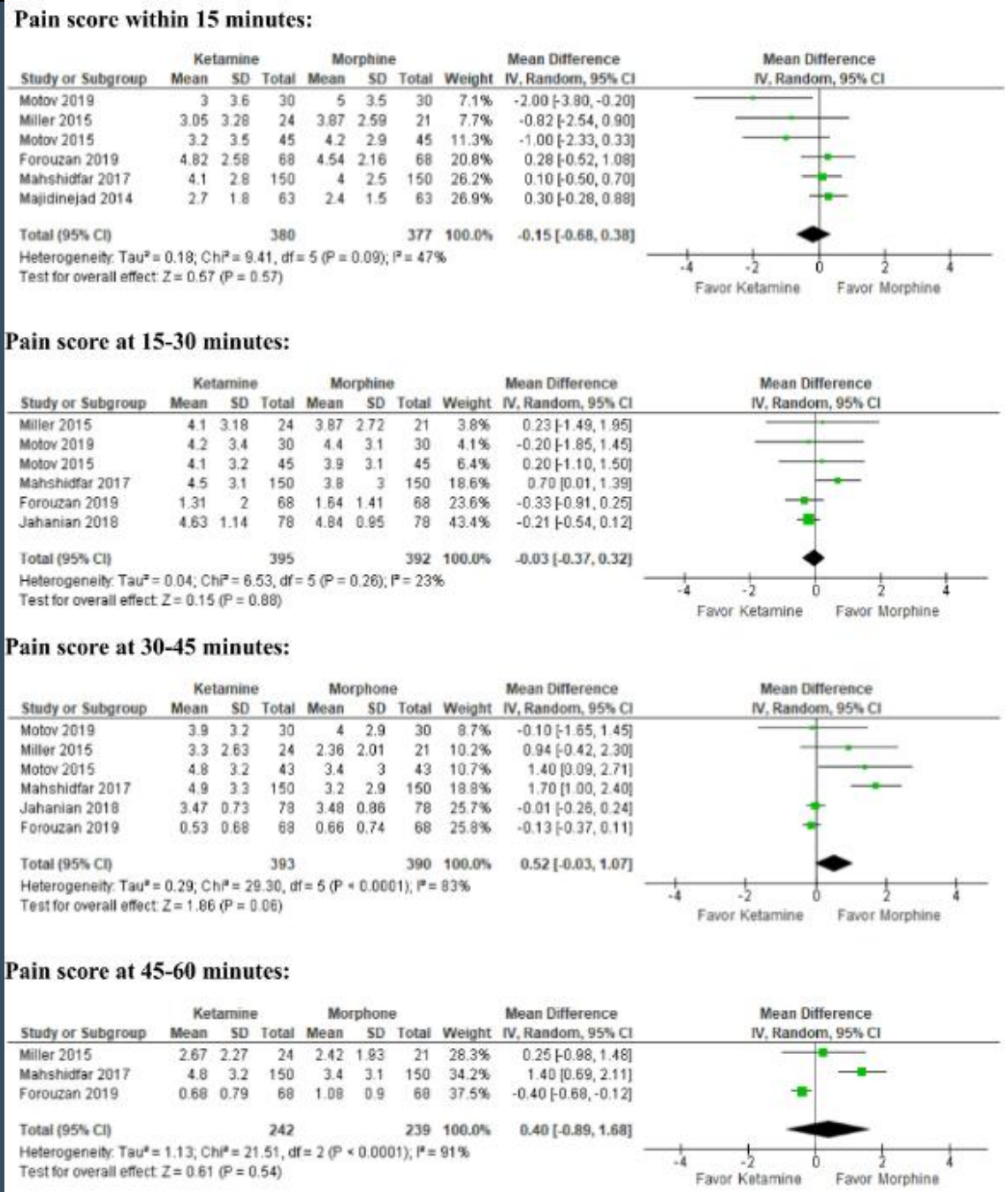
Heterogeneity: $Chi^2 = 2.12$, $df = 6$ ($P = 0.91$); $I^2 = 0\%$

Test for overall effect: $Z = 4.27$ ($P < 0.0001$)




Meta-analysis looking at ketamine when added to opioids perioperatively
Nine trials (535 adults, 60 children) reported pain intensity at rest at 24 hours and found reduces 24-h pain (−1.1 VAS) and morphine use (~−13 mg) and lowers PONV risk, without increasing hallucinations

# Acute Pain in ED



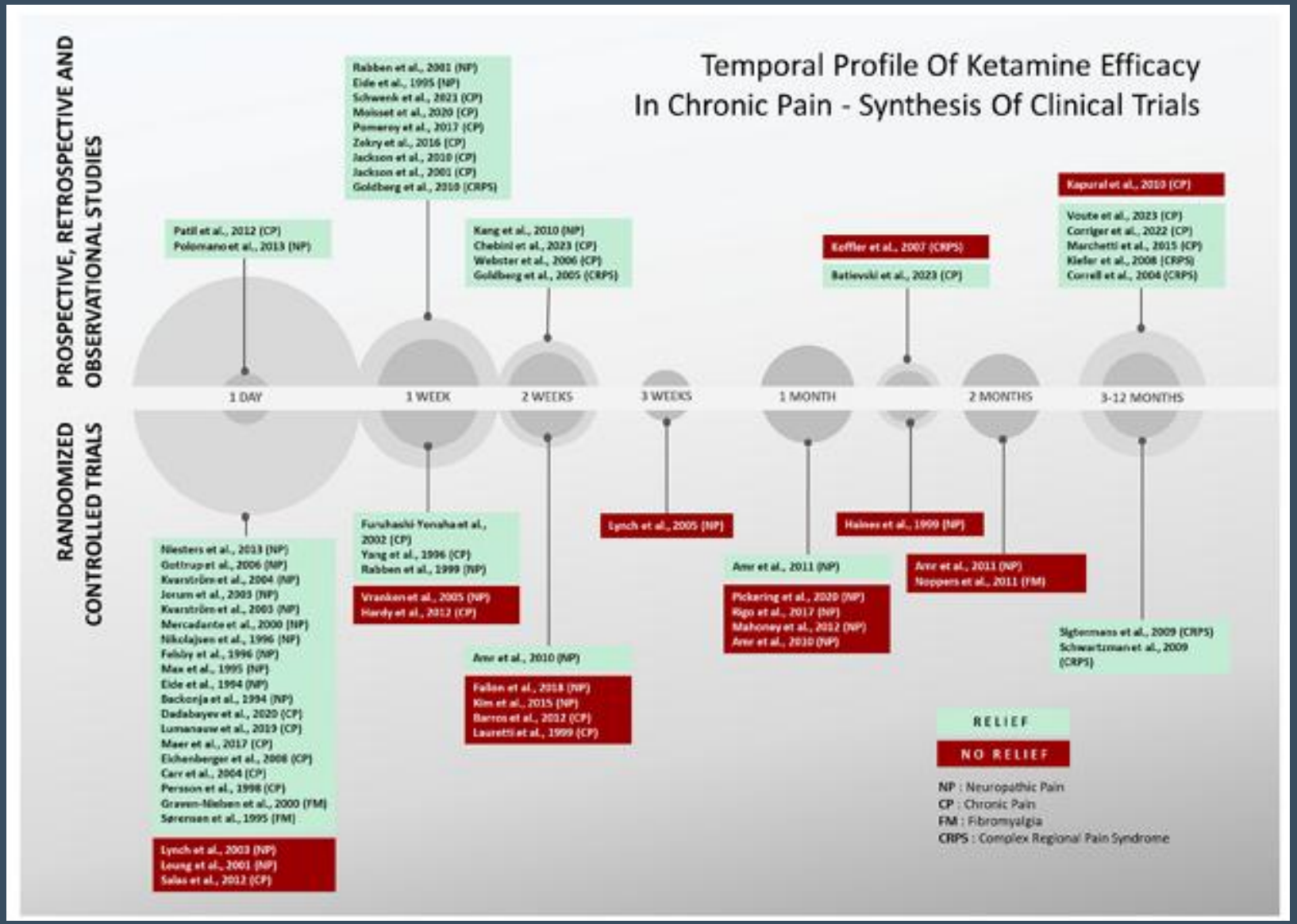


8 RCTs
1191 patients

Studies used subanesthetic ketamine doses ranging from 0.2 to 0.5 mg/kg IV.
All studies used morphine boluses of 0.1 mg/kg IV

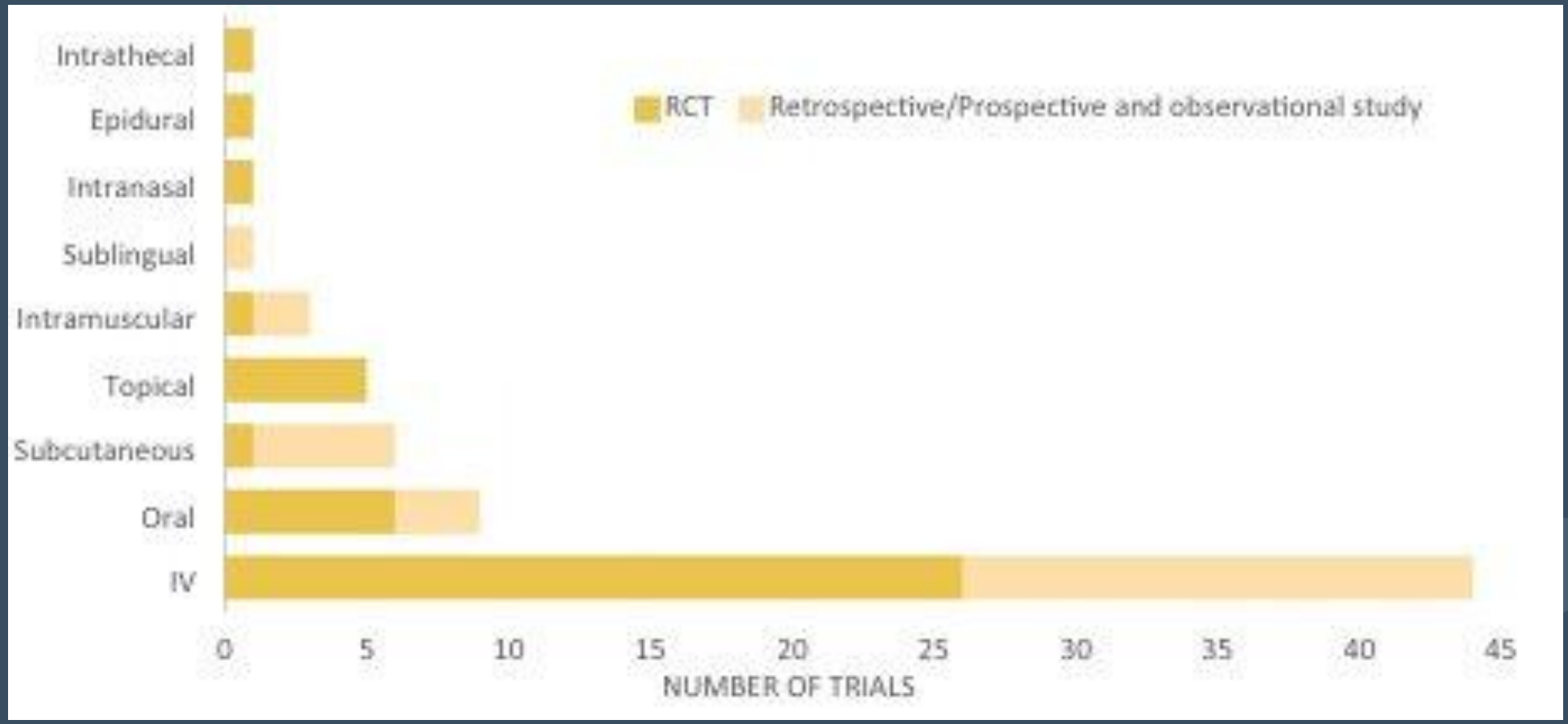
No difference up to first 60 minutes.
Morphine superior after 60 min with similar safety profile

# Chronic non-cancer pain



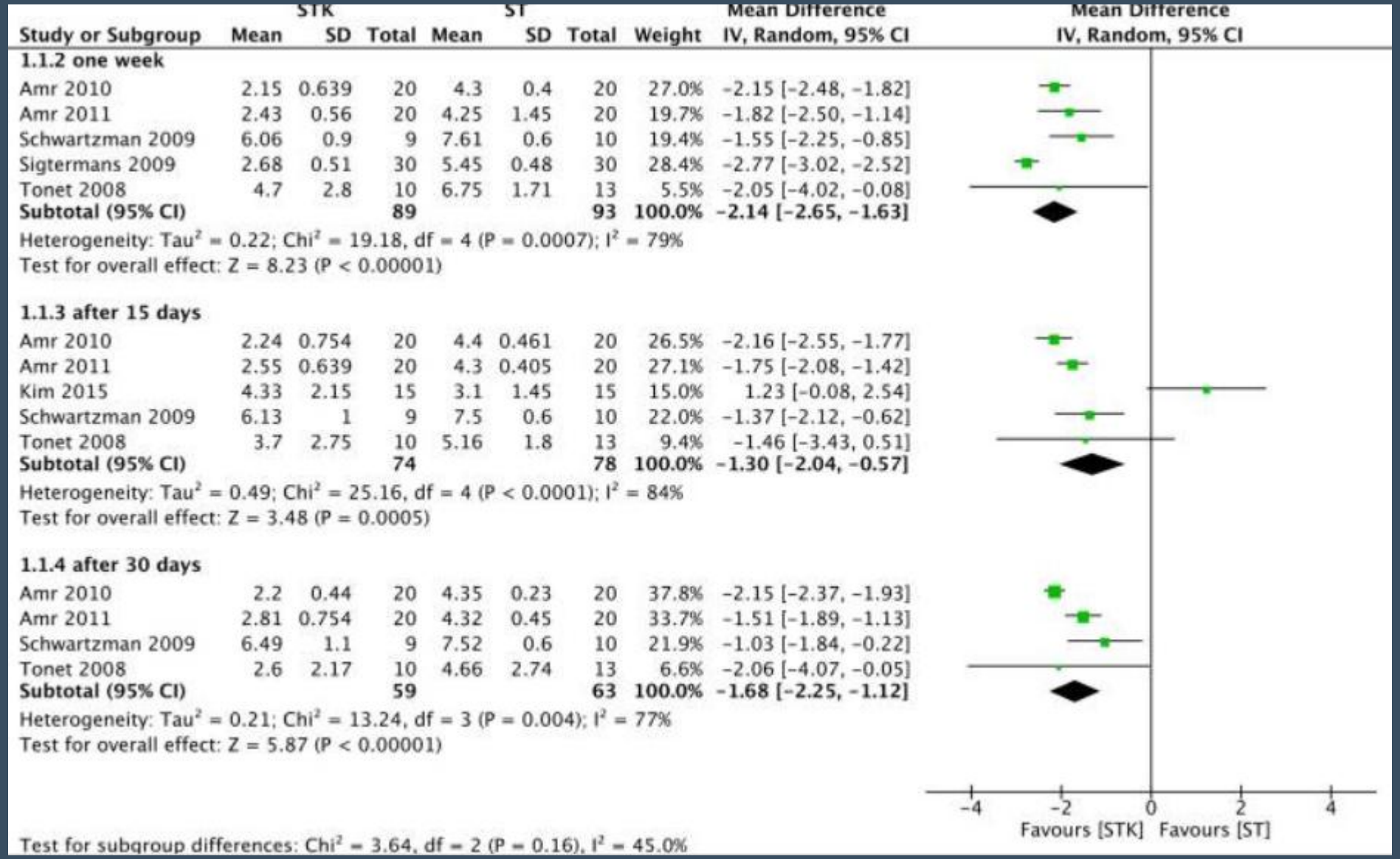

PMID: 41099780

# Chronic non-cancer pain




PMID: 41099780

# Chronic non-cancer pain (NP)



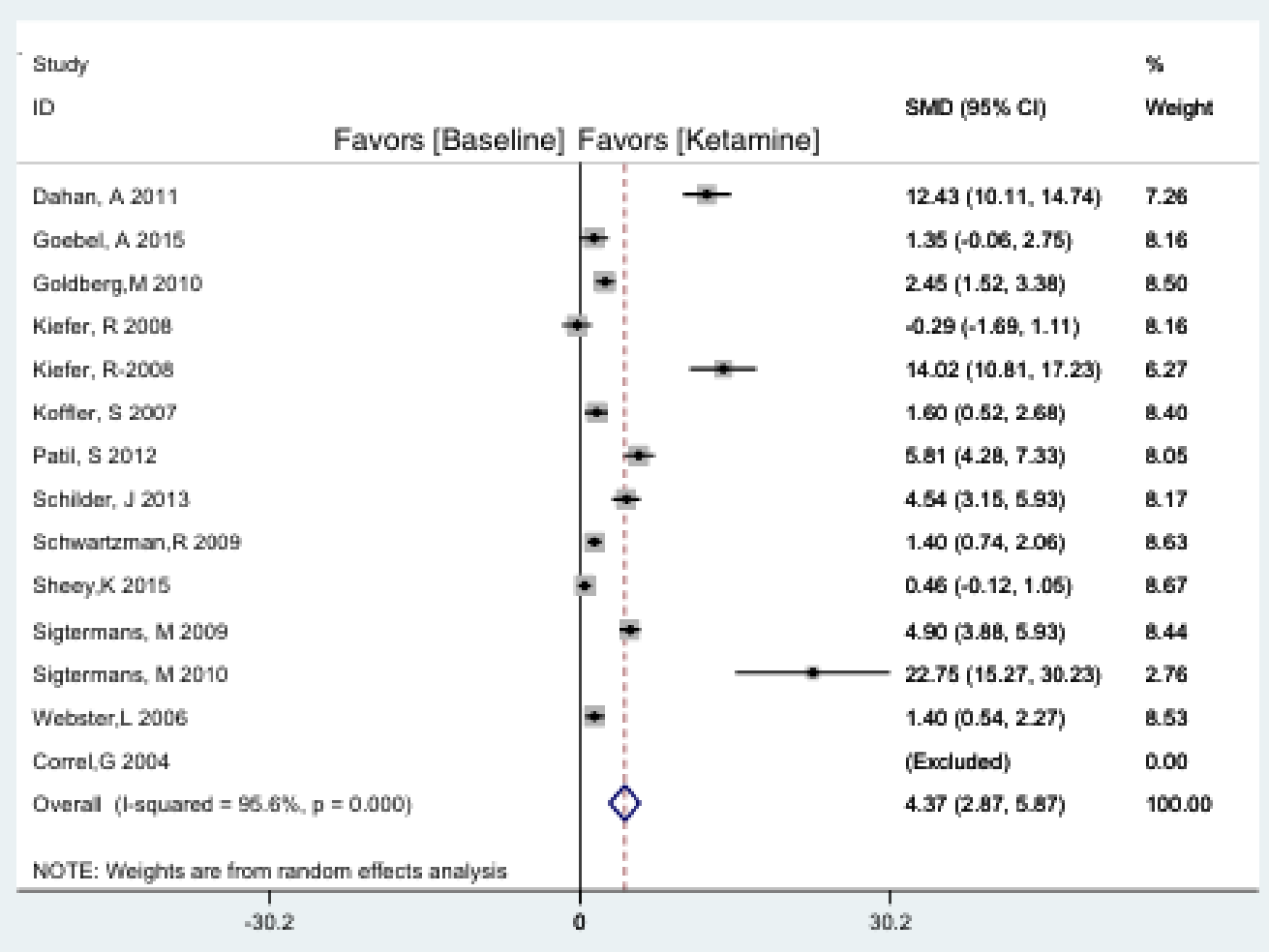
| Study or Subgroup | STK Mean | STK SD | STK Total | ST Mean | ST SD | ST Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.2 one week** | | | | | | | | |
| Amr 2010 | 2.15 | 0.639 | 20 | 4.3 | 0.4 | 20 | 27.0% | -2.15 [-2.48, -1.82] |
| Amr 2011 | 2.43 | 0.56 | 20 | 4.25 | 1.45 | 20 | 19.7% | -1.82 [-2.50, -1.14] |
| Schwartzman 2009 | 6.06 | 0.9 | 9 | 7.61 | 0.6 | 10 | 19.4% | -1.55 [-2.25, -0.85] |
| Sigtermans 2009 | 2.68 | 0.51 | 30 | 5.45 | 0.48 | 30 | 28.4% | -2.77 [-3.02, -2.52] |
| Tonet 2008 | 4.7 | 2.8 | 10 | 6.75 | 1.71 | 13 | 5.5% | -2.05 [-4.02, -0.08] |
| **Subtotal (95% CI)** | | | **89** | | | **93** | **100.0%** | **-2.14 [-2.65, -1.63]** |
| Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 19.18$, df = 4 (P = 0.0007); $I^2 = 79\%$ | | | | | | | | |
| Test for overall effect: Z = 8.23 (P < 0.00001) | | | | | | | | |
| **1.1.3 after 15 days** | | | | | | | | |
| Amr 2010 | 2.24 | 0.754 | 20 | 4.4 | 0.461 | 20 | 26.5% | -2.16 [-2.55, -1.77] |
| Amr 2011 | 2.55 | 0.639 | 20 | 4.3 | 0.405 | 20 | 27.1% | -1.75 [-2.08, -1.42] |
| Kim 2015 | 4.33 | 2.15 | 15 | 3.1 | 1.45 | 15 | 15.0% | 1.23 [-0.08, 2.54] |
| Schwartzman 2009 | 6.13 | 1 | 9 | 7.5 | 0.6 | 10 | 22.0% | -1.37 [-2.12, -0.62] |
| Tonet 2008 | 3.7 | 2.75 | 10 | 5.16 | 1.8 | 13 | 9.4% | -1.46 [-3.43, 0.51] |
| **Subtotal (95% CI)** | | | **74** | | | **78** | **100.0%** | **-1.30 [-2.04, -0.57]** |
| Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 25.16$, df = 4 (P < 0.0001); $I^2 = 84\%$ | | | | | | | | |
| Test for overall effect: Z = 3.48 (P = 0.0005) | | | | | | | | |
| **1.1.4 after 30 days** | | | | | | | | |
| Amr 2010 | 2.2 | 0.44 | 20 | 4.35 | 0.23 | 20 | 37.8% | -2.15 [-2.37, -1.93] |
| Amr 2011 | 2.81 | 0.754 | 20 | 4.32 | 0.45 | 20 | 33.7% | -1.51 [-1.89, -1.13] |
| Schwartzman 2009 | 6.49 | 1.1 | 9 | 7.52 | 0.6 | 10 | 21.9% | -1.03 [-1.84, -0.22] |
| Tonet 2008 | 2.6 | 2.17 | 10 | 4.66 | 2.74 | 13 | 6.6% | -2.06 [-4.07, -0.05] |
| **Subtotal (95% CI)** | | | **59** | | | **63** | **100.0%** | **-1.68 [-2.25, -1.12]** |
| Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 13.24$, df = 3 (P = 0.004); $I^2 = 77\%$ | | | | | | | | |
| Test for overall effect: Z = 5.87 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: $Chi^2 = 3.64$, df = 2 (P = 0.16), $I^2 = 45.0\%$ | | | | | | | | |



- 5 RCTs
- 182 pts
- Pain assessed at 1 week, 15 days and 30 days showed reduction in baseline pain of 46%

doi:10.2147/JPR.S358070

# Chronic non cancer pain (CRPS)



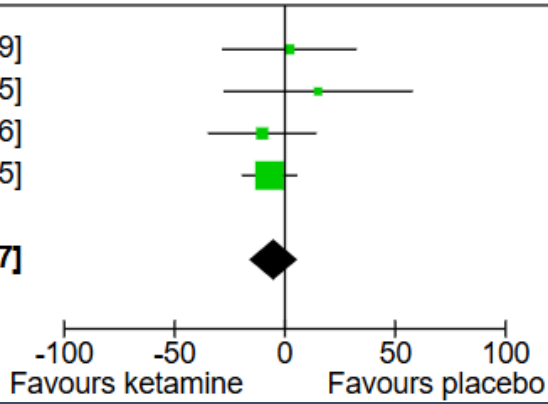

- 15 studies (RCT or cohort studies)
- 258 patients
- All studies found improved pain

PMID: 29404715.

# Chronic non-cancer pain (all types)

| Study or Subgroup | Ketamine (intravenous) Mean [0 to 100] | SD [0 to 100] | Total | Placebo Mean [0 to 100] | SD [0 to 100] | Total | Weight | Mean Difference IV, Random, 95% CI [0 to 100] |
|---|---|---|---|---|---|---|---|---|
| Noppers 2011a | 63 | 38.105118 | 12 | 61 | 38.105118 | 12 | 11.2% | 2.00 [-28.49 , 32.49] |
| Pickering 2020 | 73 | 35 | 6 | 58 | 37 | 5 | 5.7% | 15.00 [-27.85 , 57.85] |
| Schwartzman 2009 | 64.9 | 33 | 9 | 75.2 | 18.973666 | 10 | 17.2% | -10.30 [-34.86 , 14.26] |
| Sigtermans 2009 | 67 | 27.386128 | 30 | 74 | 21.908902 | 30 | 65.9% | -7.00 [-19.55 , 5.55] |
| **Total (Wald[a])** | | | **57** | | | **57** | **100.0%** | **-5.32 [-15.51 , 4.87]** |

Test for overall effect: Z = 1.02 (P = 0.31)

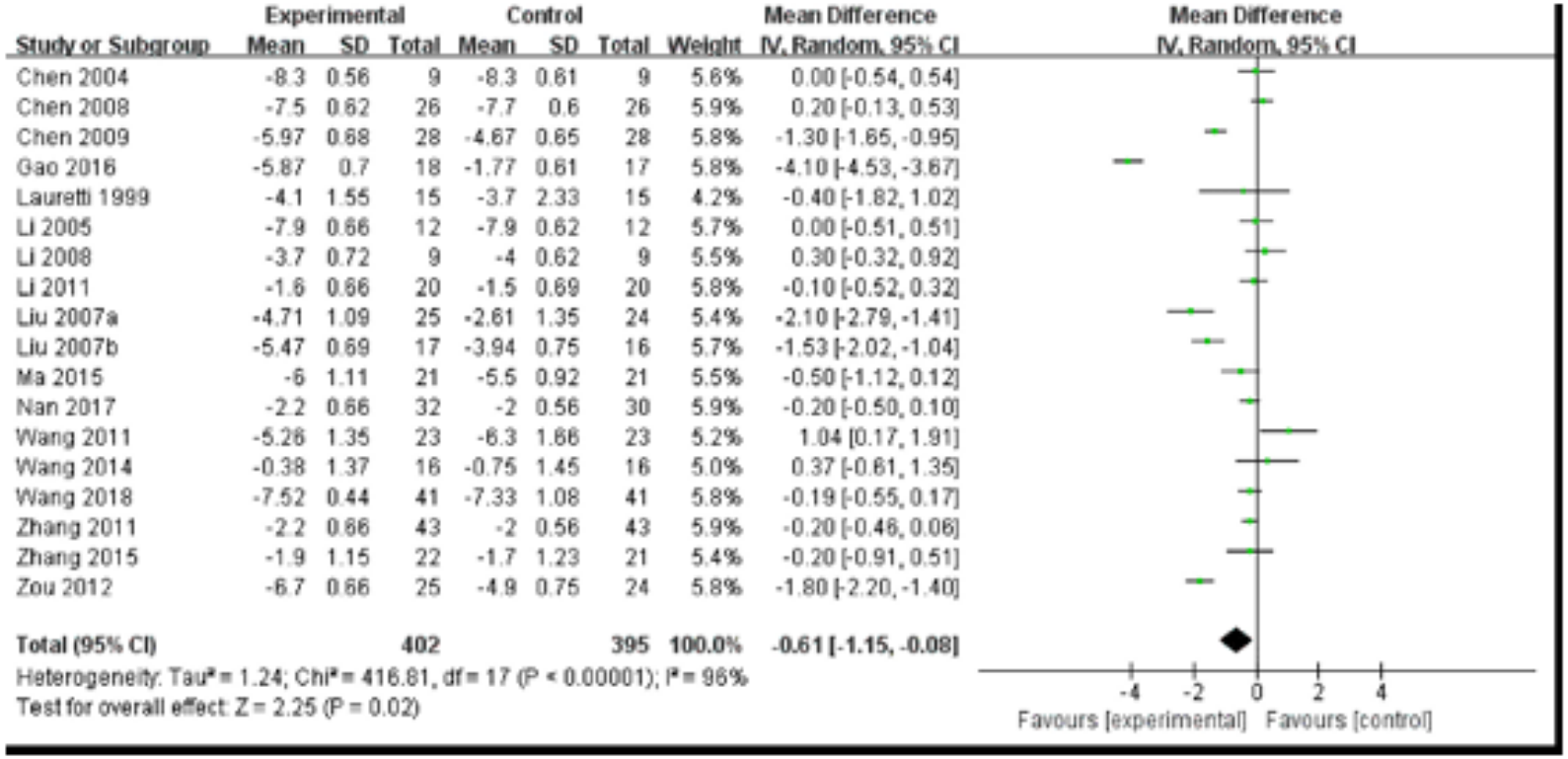



Cochrane review June 2025

Low quality evidence with significant heterogeneity

Benefits and harms of ketamine for all cause chronic pain are uncertain

# Cancer pain



| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chen 2004 | -8.3 | 0.56 | 9 | -8.3 | 0.61 | 9 | 5.6% | 0.00 [-0.54, 0.54] |
| Chen 2008 | -7.5 | 0.62 | 26 | -7.7 | 0.6 | 26 | 5.9% | 0.20 [-0.13, 0.53] |
| Chen 2009 | -5.97 | 0.68 | 28 | -4.67 | 0.65 | 28 | 5.8% | -1.30 [-1.65, -0.95] |
| Gao 2016 | -5.87 | 0.7 | 18 | -1.77 | 0.61 | 17 | 5.8% | -4.10 [-4.53, -3.67] |
| Lauretti 1999 | -4.1 | 1.55 | 15 | -3.7 | 2.33 | 15 | 4.2% | -0.40 [-1.82, 1.02] |
| Li 2005 | -7.9 | 0.66 | 12 | -7.9 | 0.62 | 12 | 5.7% | 0.00 [-0.51, 0.51] |
| Li 2008 | -3.7 | 0.72 | 9 | -4 | 0.62 | 9 | 5.5% | 0.30 [-0.32, 0.92] |
| Li 2011 | -1.6 | 0.66 | 20 | -1.5 | 0.69 | 20 | 5.8% | -0.10 [-0.52, 0.32] |
| Liu 2007a | -4.71 | 1.09 | 25 | -2.61 | 1.35 | 24 | 5.4% | -2.10 [-2.79, -1.41] |
| Liu 2007b | -5.47 | 0.69 | 17 | -3.94 | 0.75 | 16 | 5.7% | -1.53 [-2.02, -1.04] |
| Ma 2015 | -6 | 1.11 | 21 | -5.5 | 0.92 | 21 | 5.5% | -0.50 [-1.12, 0.12] |
| Nan 2017 | -2.2 | 0.66 | 32 | -2 | 0.56 | 30 | 5.9% | -0.20 [-0.50, 0.10] |
| Wang 2011 | -5.26 | 1.35 | 23 | -6.3 | 1.66 | 23 | 5.2% | 1.04 [0.17, 1.91] |
| Wang 2014 | -0.38 | 1.37 | 16 | -0.75 | 1.45 | 16 | 5.0% | 0.37 [-0.61, 1.35] |
| Wang 2018 | -7.52 | 0.44 | 41 | -7.33 | 1.08 | 41 | 5.8% | -0.19 [-0.55, 0.17] |
| Zhang 2011 | -2.2 | 0.66 | 43 | -2 | 0.56 | 43 | 5.9% | -0.20 [-0.46, 0.06] |
| Zhang 2015 | -1.9 | 1.15 | 22 | -1.7 | 1.23 | 21 | 5.4% | -0.20 [-0.91, 0.51] |
| Zou 2012 | -6.7 | 0.66 | 25 | -4.9 | 0.75 | 24 | 5.8% | -1.80 [-2.20, -1.40] |
| **Total (95% CI)** | | | **402** | | | **395** | **100.0%** | **-0.61 [-1.15, -0.08]** |

Heterogeneity: Tau² = 1.24; Chi² = 416.81, df = 17 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.25 (P = 0.02)



Fig. 2. The forest plot of VAS. 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; VAS, visual analog scale. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

18 RCTs comparing ketamine to control

Mean difference of –0.61 on VAS scale

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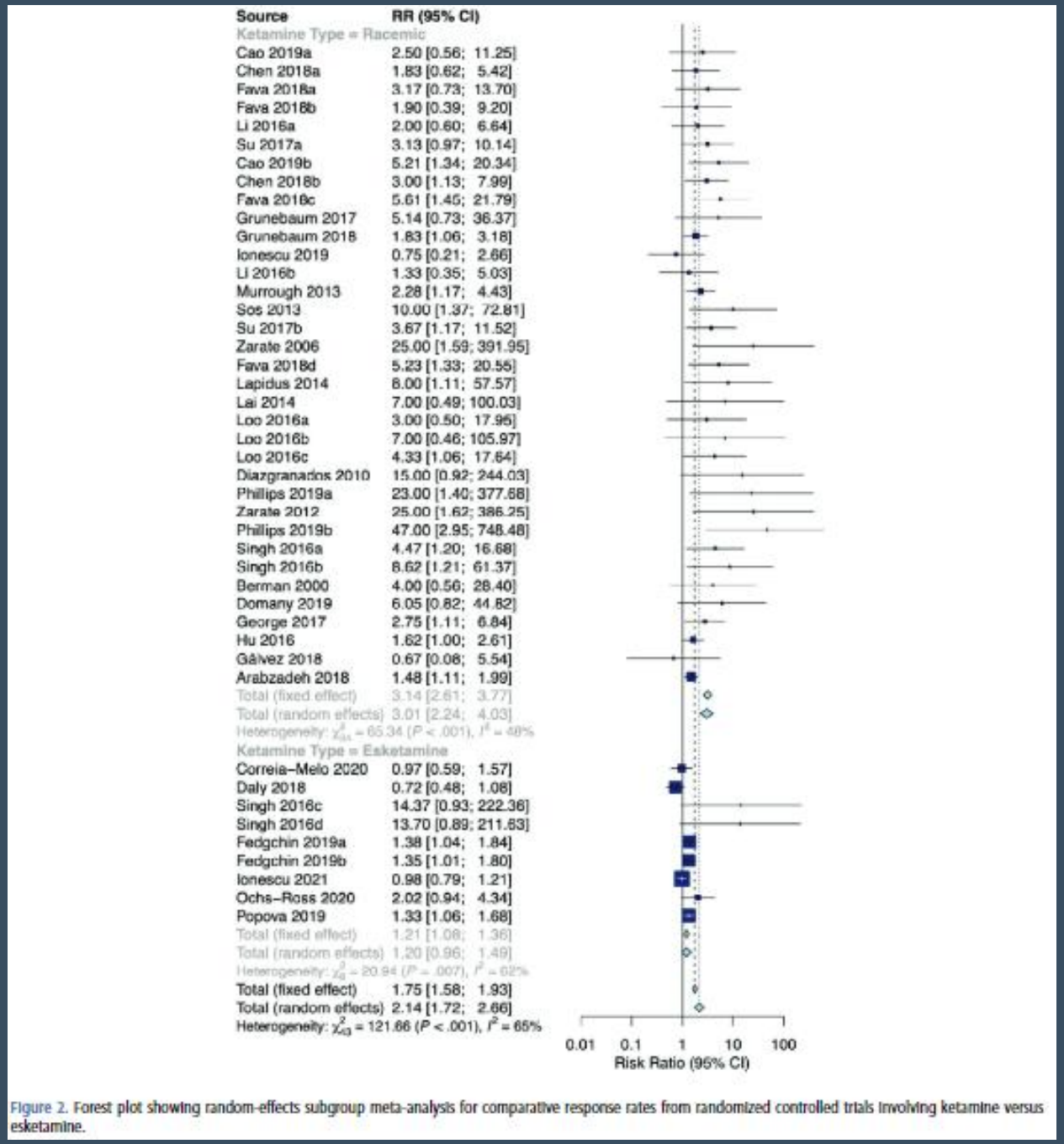


Figure 2. Forest plot showing random-effects subgroup meta-analysis for comparative response rates from randomized controlled trials involving ketamine versus esketamine.

# Depression

36 studies
2903 patients
9 trials used esketamine
27 used racemic ketamine

Overall, ketamine (pooled for racemic and esketamine) was associated with improved end-of-treatment response, remission, and depression severity against placebo

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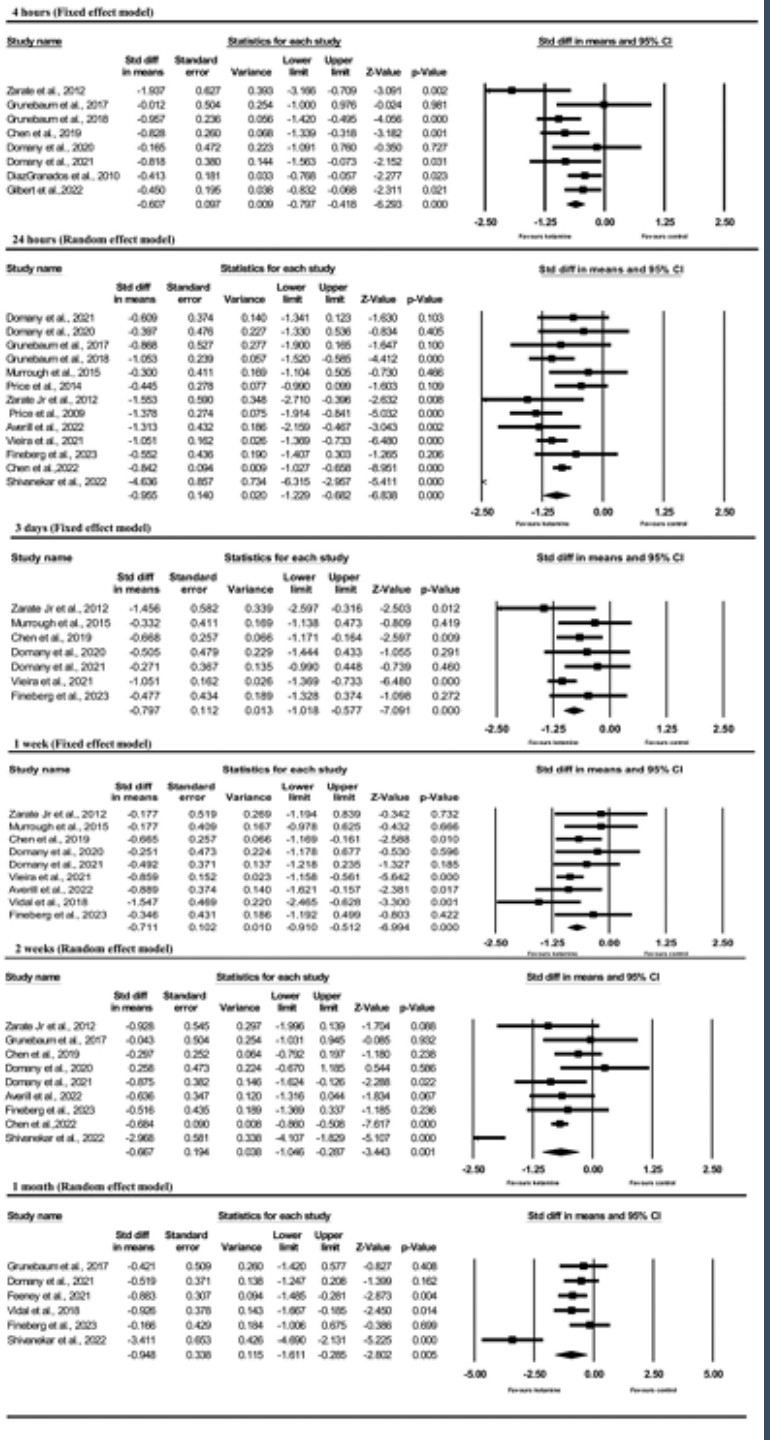
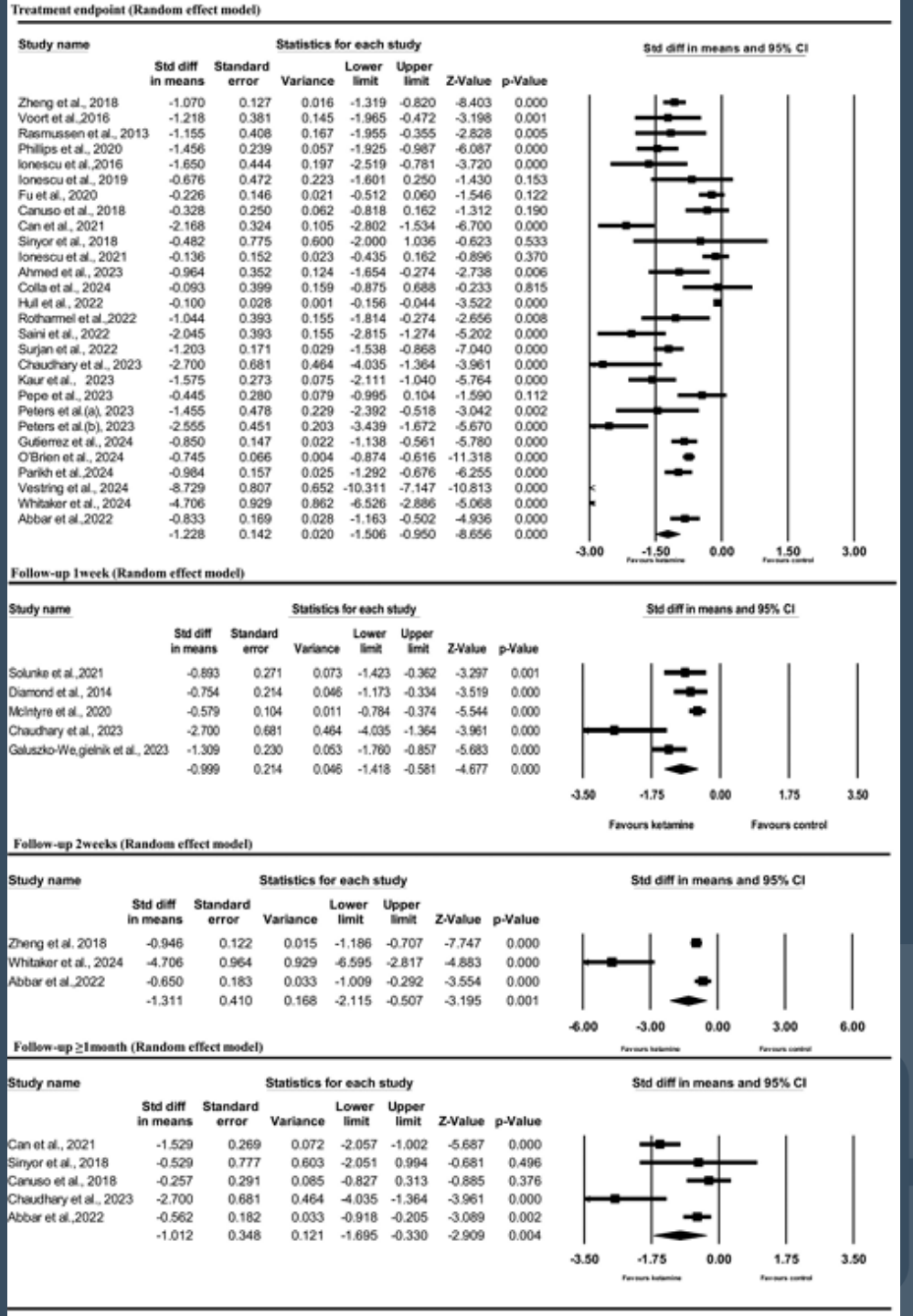



# Suicidal Ideation

- 49 clinical trials
- 3982 pts
- Sig benefit at 4 h lasting 1 month



# What does the (low quality) evidence tell us?

- Acute pain – effective
- Chronic pain
  - Neuropathic pain – effective
  - CRPS – effective
  - Fibromyalgia – limited data to support (3 trials)
  - Other chronic nociceptive pain – not likely effective
  - Anti – hyperalgesia – very limited studies (1 RCT, case reports)
- Cancer pain – effective
- Treatment refractory depression - very effective
- SI - very effective
- IV > PO

# What are the limitations of the evidence?

- Significant heterogeneity
  - Dose
  - Route
  - Duration
  - Pain/mood phenotype
- Low quality -> Inherent difficulty in developing robust RCT given nature of psychomimetic fx
- Unclear safety long term

# Objectives

1. Briefly review history of ketamine's development
2. Understand unique pharmacology of ketamine
3. Appreciate safety and toxicity concerns
4. Review evidence for its use in treating pain and mood disorders
5. Identify appropriate patient candidates and formulate dosing strategies

# Patient selection in Serious Illness

- Acute pain
  - Perioperative; vaso-occlusive crises in SCD; pathologic fracture
- Poorly controlled neuropathic pain despite opioid titration and co-administration of non-opioid adjuvants from several classes
- Significant depression with life-limiting prognosis despite standard treatments
- Cancer pain refractory to multimodal interventions
- Treatment refractory depression or active SI
  - Best done in collaboration with psychiatry
- Opioid induced hyperalgesia / allodynia

# Dosing Protocols

- Intravenous
  - 0.1 - 1 mg/kg/day
    - Lack of consensus in optimal duration and protocol with published data ranging from 40 min to hours/days
    - CC protocol: 0.5 mg/kg over 40 min for 5 days
- Oral
  - 10 mg PO TID titrate to effect by 10 mg per dose per day
  - 0.5 mg/kg daily
  - Typical ranges 20 – 400 mg/d
- Intranasal
  - 84 mg, standard dose Spravato (esketamine). REMS required. 8 doses in office fist month then every week to week 8 then q1-2 weeks
- Avoid co-administration with haloperidol or benzodiazepine to reduce likelihood of psychomimetic effects

Standardized ketamine infusion protocol for chronic refractory pain: a retrospective study of preliminary effectiveness and treatment completion

Hallie Tankha [1,2] Sara Davin,[3] Brittany Lapin,[4,5] Yadi Li,[4,5] Austin Kennemer,[6] Andrew Schuster,[5] Jijun Xu [2,7,8] Raghavan Gopalakrishnan,[9] Pavan Tankha[3]

PMID: 35092320

https://www.palliativecareguidelines.scot.nhs.uk/guidelines/medicine-information-sheets/ketamine.aspx

# Barriers

- Structural
  - Pharmacy availability
  - Infusion availability
  - Cost
    - IV infusions not covered ($400-1200 per infusion)
    - PO generic ketamine ~one dollar per mL
    - Spravato ~$700 per dose (8 doses first month then weekly thereafter)
      - REMS required; must be administered in clinic with caregiver accompanying pt
- Individual
  - Stigma – off label use
  - Psychomimetic AE with prior use
  - Medical contraindications

# Next steps

- Standardize dosing protocols
- More research on non-IV routes
- Clarify long term safety (addiction, cognition)
- Encourage payor changes
- Phenotyping patients on basis of pain type, intensity and comorbidities

Cleveland Clinic

# A Spoonful of Ketamine Makes Chronic Pain Go Down!

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## OBJECTIVES

- Identify candidates for whom the initiation of oral ketamine as an adjuvant analgesic for the management of chronic pain is appropriate.
- Appreciate the efficacy and safety of chronic oral ketamine use as an adjuvant to methadone for the treatment of chronic pain.

## BACKGROUND

- Chronic pain is defined as any pain that persists or recurs for at least 3 months and is often multifactorial with deleterious impacts on quality of life (1).
- There is evidence that ketamine, an n-methyl-d-aspartate (NMDA) receptor antagonist approved by the FDA for induction and maintenance of general anesthesia and for treatment refractory depression, may be efficacious for the management of certain chronic pain conditions (2).
- Through its action on the NMDA receptor, ketamine is thought to reduce the amplification of pain responses that can occur in the setting of repeated pain stimuli that occur in chronic pain, addressing what is known as the "wind-up phenomenon" (3).
- However, data on the use of subanesthetic ketamine for management of chronic pain is mostly limited to intravenous administration and lacks clarity on long term efficacy (4).
- Additionally, access to subanesthetic intravenous ketamine is limited by logistical, regulatory, and payor challenges (5).
- Recent findings suggest that oral ketamine may be an effective, well-tolerated, and more easily accessible option for the management of chronic pain (6).
- However, there are still significant gaps in the evidence supporting the safety and efficacy of long-term oral ketamine.

## CASE PRESENTATION

- 39-year-old man with a medical history of acute lymphoblastic leukemia diagnosed in 1999 and treated with chemotherapy and whole brain radiation, with subsequent relapse in 2016 for which he ultimately underwent allogenic bone marrow transplant in 2017.
- His BMT was complicated by the development of severe chronic graft versus host disease for which he has been treated with multiple GVHD regimens without response.
- The primary manifestation of his chronic GVHD included severe skin sclerosis and wounds (Figure 1), which resulted in a chronic pain syndrome for which he was referred to outpatient Palliative Medicine.

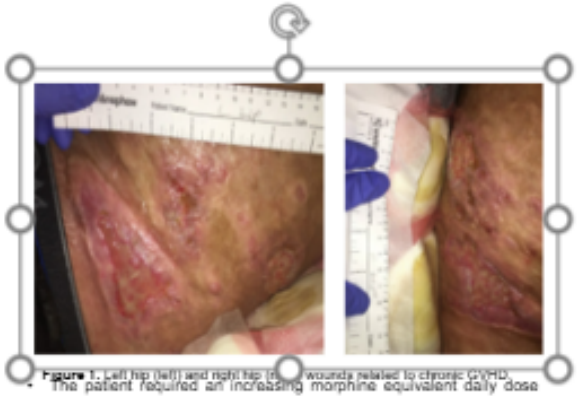

**Figure 1.** Left hip (left) and right hip (right) wounds related to chronic GVHD.

- The patient required an increasing morphine equivalent daily dose (MEDD) for uncontrolled pain in the setting of progressive disease.
- His adjunctive pain medications were also optimized – including trials of meloxicam, gabapentin, pregabalin, diclofenac, topiramate, duloxetine, and steroids – and his opioids were rotated multiple times.
- He was evaluated by a chronic pain clinic for an intrathecal pump and determined not to be a candidate due to diffuse pain. Other interventional pain modalities, such as epidural steroid injections, were done to reduce overall pain burden without benefit.
- Despite the use of a combination of interventional, adjuvant, and opioid therapies, his MEDD on methadone therapy eventually exceeded 700 mg and his pain remained uncontrolled.
- Therefore, a decision was made to start oral ketamine liquid solution at 0.25 mg/kg twice daily given its efficacy as an adjuvant when combined with methadone (7).

## OUTCOMES

- Following the initiation of oral ketamine, the patient's MEDD fell gradually over the next 15 months until a nadir of less than 300 mg (Figure 2).
- Compared to the three months before starting and after stopping ketamine therapy, the patient's pain score decreased by greater than 2 points on a numerical rating scale (Figure 3).
- There were no reported treatment-related adverse effects as described in the literature, including cystitis or hepatitis.
- Treatment was interrupted twice and ultimately discontinued due to financial toxicity (~$180/month).


**Figure 2.** Patient total MEDD over time with associated approximate ketamine start dates (green circles) and stop dates (red squares).

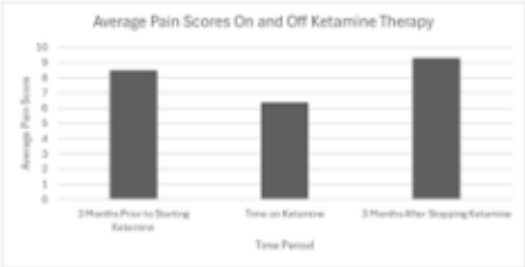


**Figure 3.** Average patient-reported pain score taken from 3 months prior to initiation of ketamine therapy, from time spent on ketamine therapy, and from 3 months after stopping ketamine therapy.

## DISCUSSION

- This case demonstrates that the addition of twice daily oral ketamine to methadone for chronic, refractory pain correlated with a gradual reduction in the patient's total MEDD by more than 50%, along with a clinically meaningful improvement in average patient reported pain intensity as seen by a reduction of greater than 2 points on a standard numerical rating scale sustained during treatment.
- The patient tolerated the therapy for more than one year without any noted adverse effects. This result is consistent with emerging evidence that suggests that oral ketamine may be an effective, well-tolerated, and accessible adjunct to methadone for the treatment of chronic pain syndromes refractory to escalations in opioid therapy(6-8).
- Further studies showing the efficacy and safety of oral ketamine for the management of varied chronic pain syndromes are needed to support systemic reforms, including regulatory and commercial incentives to encourage pharmaceutical production of ketamine and payor coverage as well as the development of clinical guidelines to guide prescribing.

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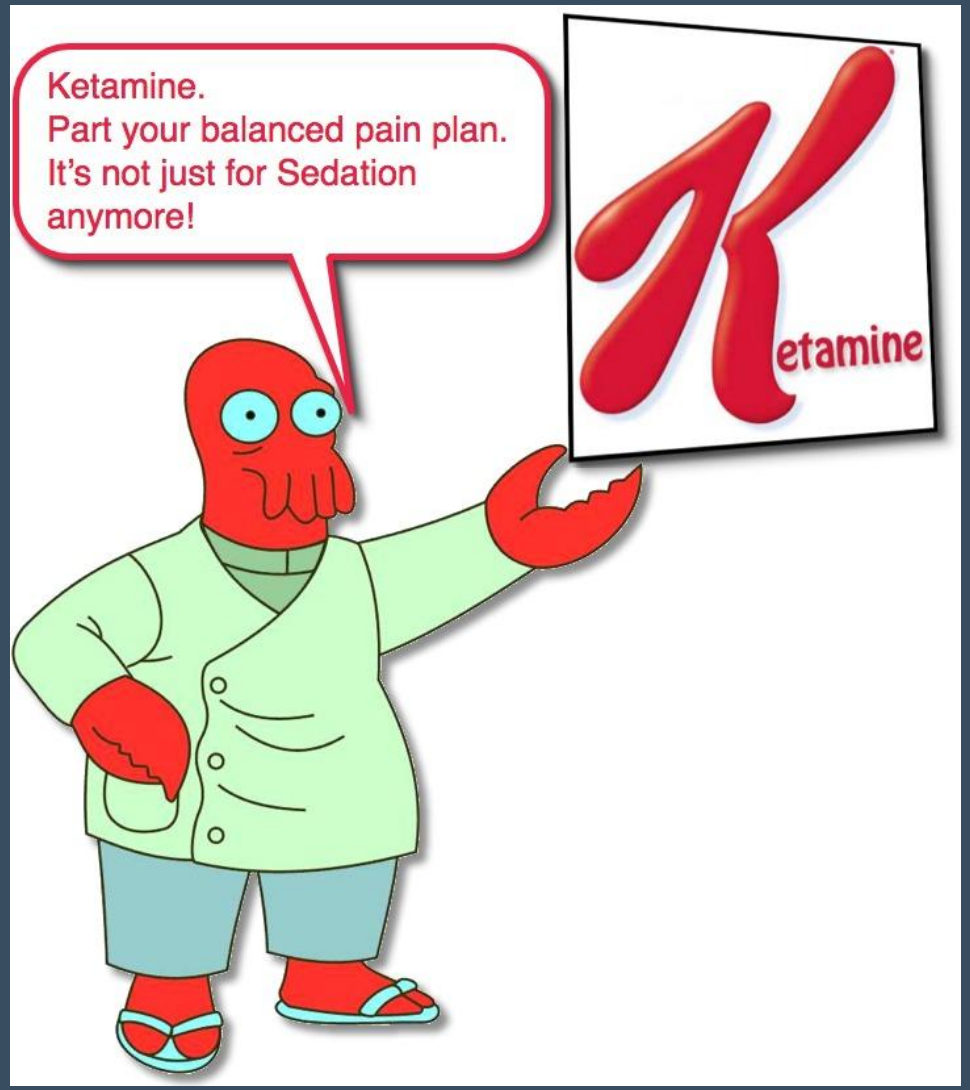
# Thank you!




"To know ketamine is to love ketamine"

https://pedemmorsels.com/ketamine-analgesia/