The Role of Ketamine in the Management of Complex Acute Pain

Dr James Bennett
Consultant Anaesthetist
Consultant Lead for Inpatient Pain Service
East Sussex Healthcare NHS Trust
STAPG Committee Member

Dr Gillian Chumbley

- Consultant Nurse – Pain Service
- Imperial College Healthcare NHS Trust
- Permission to use information within her slides

Aim of the session

- Adverse effects of ketamine abuse
- Normal pain transmission
- Changes with persistent pain
- How to use ketamine
- Does it prevent persistent pain

Adverse Effects of Ketamine

Adverse Effects

- Clinical use often limited by **dose dependent** side effects
- Studies report short term results only
- Evidence for long term clinical efficacy and safety is lacking

Adverse Effects

Dizziness
Sedation
Nausea
Agitation
Hallucinations
Nightmares

Longer Term Adverse Effects

- Rat model (Olney et al 2002)
  - Hyperstimulant effect of repeated low dose ketamine
- Canine model (Schug et al. 2015)
  - Abnormal histological changes in neural tissue with intrathecal ketamine infusion
- Neuropathic pain clinic patients (Cvrcek et al. 2008)
  - 3 months of ketamine: dry mouth, dizziness, drowsiness

Long term Effects

- Cognitive and Emotional Function
- ‘Ketamine Cystitis’
- Chronic Abdominal Pain
- Hepatotoxicity
- Abuse potential

Bladder problems / ‘Ketamine Cystitis’

- Cause unknown
- Associated with abuse
- Over 3 months use/high doses
- Ulcerative cystitis, obstructive nephropathy
- 3 cases in palliative care
- 1 case in chronic pain (Bell 2012)
- Not seen in low-dose, short duration

Bell RF. Ketamine for chronic noncancer pain: concerns regarding toxicity. Curr Opin Support Palliat Care 2012; 6: 183–7

Abuse Potential

- Most common abused drug in SE Asia
- Relationship between chronic pain and problematic drug use is complex
- Problematic drug use of prescription analgesic drugs is a major healthcare problem in Western countries

Abuse potential: Australia

- 15 x opioid prescription increase from 1992 to 2012

- Opioid related hospitalisation
  - Prescription drug use > Heroin abuse since 2001

- Opioid related deaths: 0.78 to 1.19 per 100,000 population in 10 years

Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. Br J Clin Pharmacol 2014; 78: 1159–66

How does Ketamine work?

The NMDA Receptor

- Ion channel complexes located centrally and peripherally in the nervous system
- Ligand gated ion channels (glutamate)
- Multiple functions in the nervous system

The NMDA Receptor

- Learning and Memory
- Cognitive functions
- Neural development / synaptoplasticity
- Addiction
- Psychiatric disorders
- Nociception

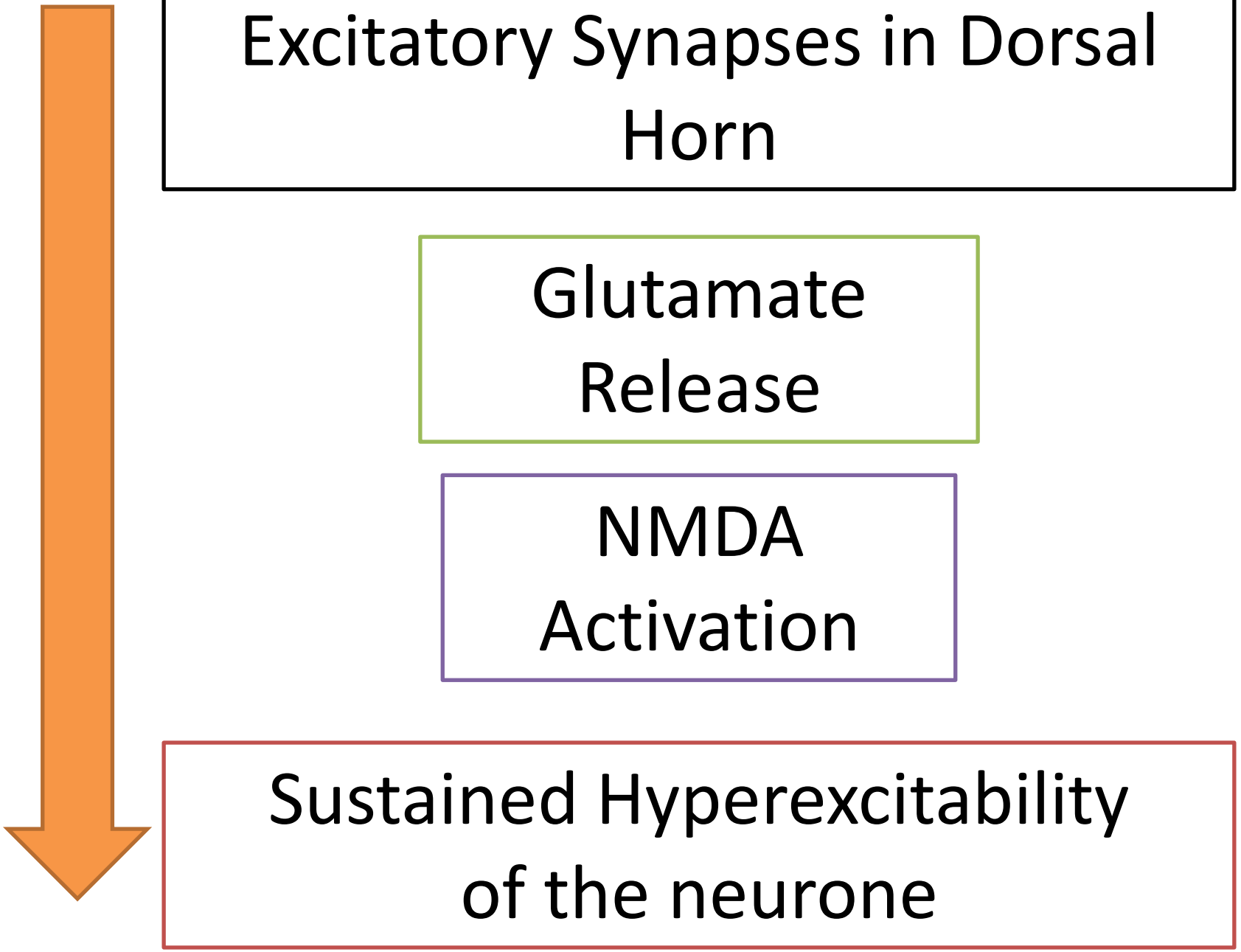
The NMDA Receptor

- Learning and Memory
- Cognitive functions
- Neural development / neuroplasticity
- Addiction
- Psychiatric disorders
- Nociception

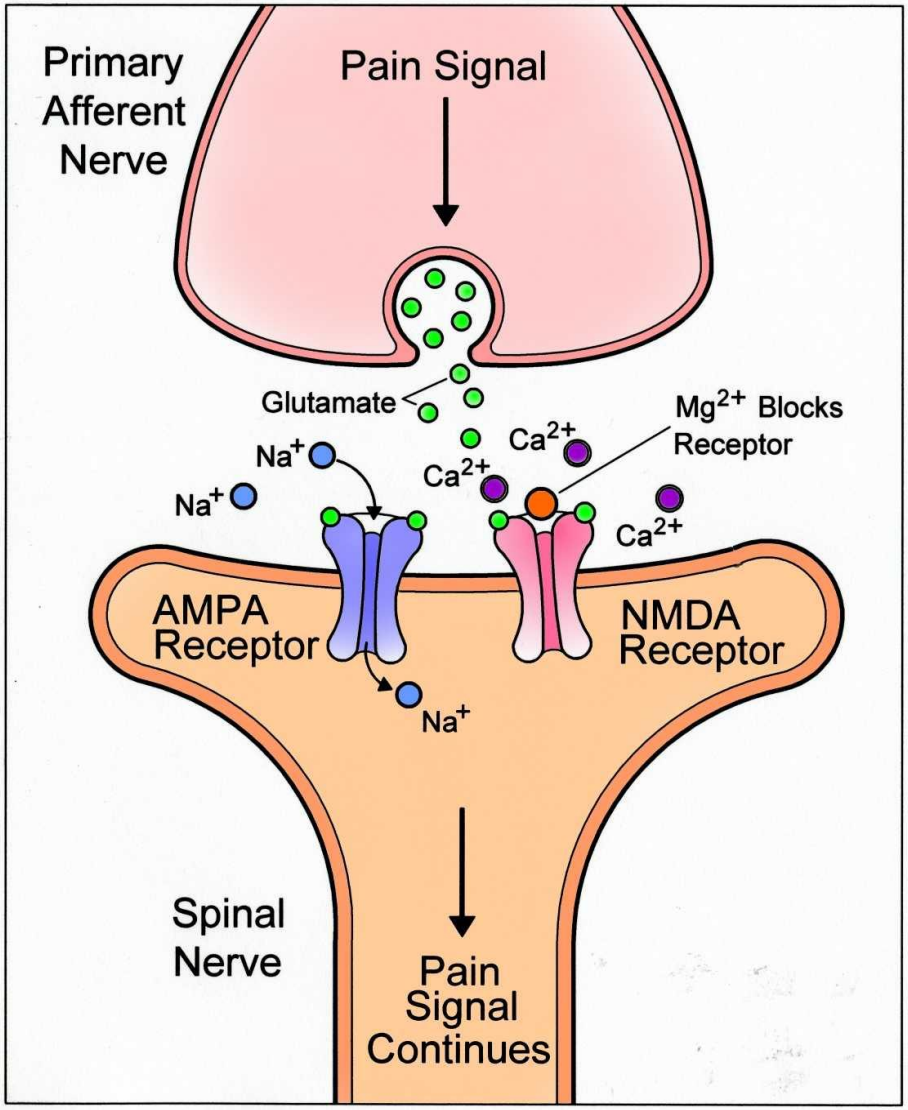
NMDA receptor – spinal level

- Activation of the receptor clinically
  - Central Sensitisation
    - Hyperalgesia
    - Allodynia
- **Amplification of nociceptive traffic** towards higher brain centres

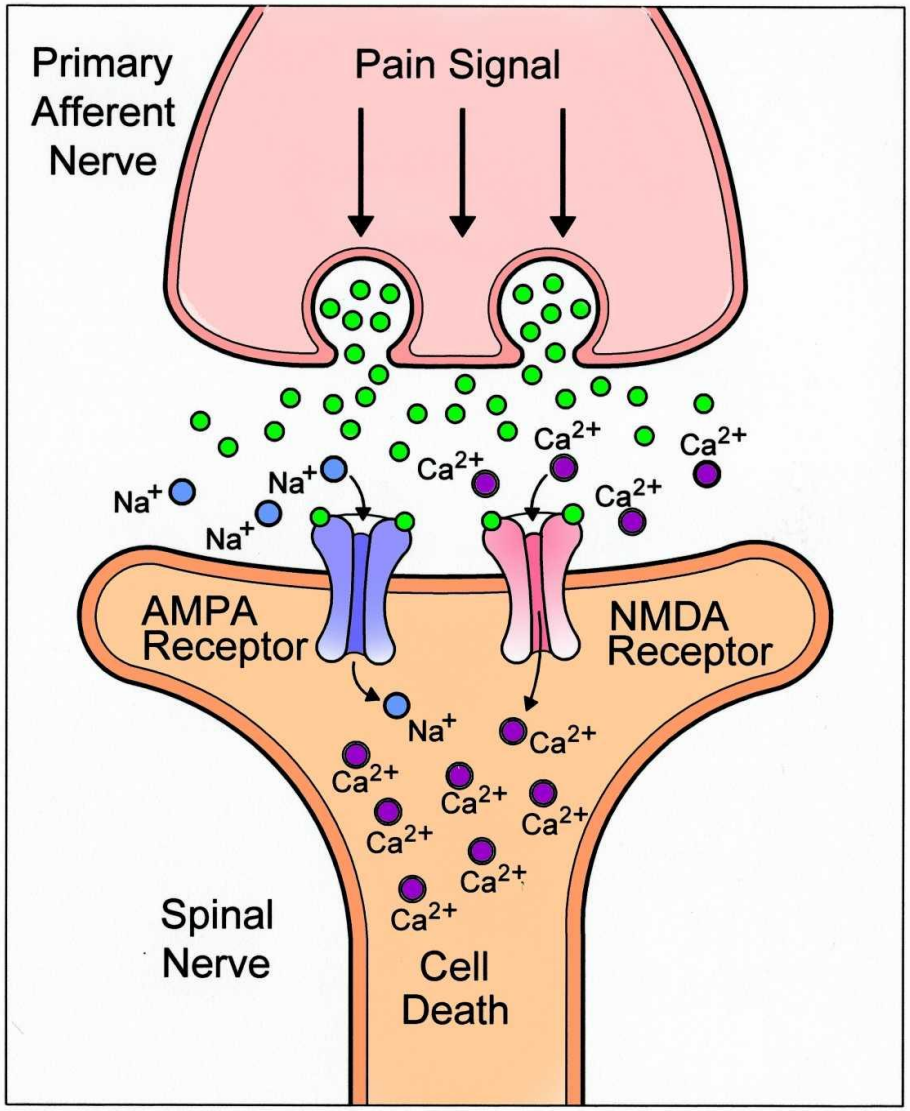
Petrenko AB, Yamakura T, Sakimura K et al (2014) Defining the role of NMDA receptors in anesthesia: are we there
yet? Eur J Pharmacol 723: 29–37


Excitatory Synapses in Dorsal Horn
Glutamate Release
NMDA Activation
Sustained Hyperexcitability of the neurone

NORMAL PAIN TRANSMISSION



ABNORMAL PAIN TRANSMISSION



Sustained Hyperexcitability of the neurone

- Acute Pain States
- Chronic Pain States
- Opioid Induced Tolerance
- Hyperalgesia / Opioid Induced Hyperalgesia

NMDA Receptor Antagonists

- Ketamine
- Magnesium
- Dextromethorphan
- Anamtadine
- Memantine

Suzuki M (2009) Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anaesthesiol* **22**(5): 618–22

NMDA Receptor Antagonists

- Ketamine
- Magnesium
- Dextromethorphan
- Anamtadine
- Memantine

Suzuki M (2009) Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anaesthesiol* **22**(5): 618–22

Ketamine

- First synthesized in the 1960's
- Dissociative anaesthetic agent
- Low-doses used for pain relief
- Blocks NMDA receptor

Ketamine Action

- In low doses acts primarily as a non-competitive antagonist of the NMDA receptor
- Slow ‘off rate’ causing a prolonged tonic block
- Main role is an adjuvant in pain associated with central sensitisation

Central Sensitisation

- Severe Acute Pain
- Neuropathic Pain
- ‘Opioid Resistant’ Pain

Persson J (2013) Ketamine in pain management. *CNS Neurosci Ther* **19**(6): 396–402.

Evidence for Ketamine?

Ketamine - evidence

- Preventative analgesia
- Peri-operative for acute post-operative pain
- Postoperative analgesia
- Postoperative analgesia, intravenous infusion
- Ketamine addition to PCA
- Opioid induced hyperalgesia

Role of NMDA receptor antagonists in preventative analgesia

- Preventative analgesia
  - Postoperative period
  - ↓Pain scores / ↓analgesic consumption
  - Relative (another Rx, no Rx, or placebo)
  - Effect observed beyond drug duration of action (>5.5 half lives)
  - Given pre-incision (pre-emptive) or intraop

McCartney C.J., Sinha A., Katz J. (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesthesia & Analgesia 98(5):1385-1400.

Role of NMDA receptor antagonists in preventative analgesia

- Preventative analgesia
  - McCartney et al. 2004
  - 24 ketamine studies
  - 58% studies showed significant preventative effect

McCartney C.J., Sinha A., Katz J. (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesthesia & Analgesia 98(5):1385-1400.

Role of NMDA receptor antagonists in preventative analgesia

- Preventative analgesia
  - McNicol et al. 2014
  - perioperative ketamine use for more than 24 h has a modest but statistically significant reduction in the incidence of persistent post-surgical pain
  - at 3 months and 6 months after operation
  - but not 12 months after surgery.

McNicol ED, Schumann R, Haroutounian S. A systemic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand 2014; 58: 1199–213

Perioperative ketamine for acute postoperative pain

- Laskowski (2011)

- 70 RCTs (ketamine bolus or infusion - subanaes)
- No RA
  - ↓opioid consumption
  - Longer time to first analgesia
- 25/32 (78%) Treatment Group had less pain
- Thoracic, Upper GI, Major Ortho
- SEs:
  - less PONV but ↑ psychomimetic effects
  - No ↑ sedation

Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011; 58: 911–23

Ketamine & PCAs

- Mathews et al 2012 (5 RCTs n=243)
- Addition of ketamine to PCA
- Post thoracotomy
  - Opioid sparing
  - Improved analgesia
  - Better Respiratory outcomes
  - Better patient satisfaction

Mathews TJ, Churchhouse AM, Housden T et al. Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interact Cardiovasc Thorac Surg 2012; 14: 194–9

Low dose IV infusion for postoperative pain

- Jouguelet-Lacoste et al 2015

- 5 meta-analysis & 39 clinical trials (Nov 2013)
  - Reduces opioid consumption by 40%
  - Lowers pain scores
  - No major complications (≤ 48 hours)

Jouguelet-Lacoste J., La Colla L., Schilling D., Chelly JE. (2015) The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: A review of the current literature. *Pain Medicine* 16:383-403.

Ketamine and Opioid induced hyperalgesia (OIH) & tolerance

- OIH
  - Nociceptive hypersensivitiy caused by exposure to opioids.
  - Paradoxical ↑ dose = ↑ pain
  - Acute: post-remifentanil
- Tolerance
  - Increasing dose of opioid is required to achieve same clinical effect

Ketamine and OIH & tolerance

- Wu 2015 (14 RCTs, n=729)
- Acute tolerance post remifentanil use
- Included ketamine (8), Mg (5) and amantadine (1) versus placebo
  - ↓ postoperative pain scores
  - ↓ opioid requirements
  - ↑ to first analgesic request
  - Better patient satisfaction

Wu L, Huang X & Sun L (2015) The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain inten sity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis. *J ClinAnesth* **27**(4): 311–24.

How to use Ketamine

Ketamine

- Used as a racemic mixture - Ketalar®

- Different concentrations
  - 10mg/ml
  - 50mg/ml
  - 100mg/ml

Ketamine

- Multiple routes
  - Bioavailability
    - IM – 93%
    - Intranasal 50%
    - Rectal – 25%
    - Oral – 20%
- Liver metabolism – norketamine (20% analgesia)

Patient Selection

- Indications for using ketamine
- **Neuropathic Pain** (inc. phantom limb)
- **Pathological Pain** (hyperalgesia, allodynia)
- **Poor opioid responsiveness**
- Patients with **previous opioid consumption**

Schug S.A. (2004) New Uses for an Old Drug: The Role of Ketamine in post-operative pain management. *ASEAN Journal of Anaesthesiology* 5(1):39-42.

Trial of Ketamine

- Intravenous (rescue) bolus
  - 2.5mg up to a maximum of 10mg

- Maintenance
  - IV infusion of 0.1 mg/kg/hour
  - Oral suspension 25mg 4 to 6 hourly
  - **Max 450mg a day**

Ketamine in complex patients

- Titrate as necessary
- May require gabapentinoid
- Decrease opioids first, avoid rebound hyperalgesia

- Don’t send them home with ketamine

- Chronic pain clinic follow up?

Can we use ketamine to prevent persistent post-surgical pain

Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacotherapy for the prevention of chronic pain after surgery in adults (Review)

Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I

Pharmacotherapy for the prevention of chronic pain after surgery in adults

- Chaparro 2013
- Ketamine – 14 RCT, small numbers (n=1388)
- Perioperative ketamine compared to placebo significantly reduces the incidence of CPSP
- at 3 months only if infusion > 24 hours
- At 6 months (even if <24hrs) [10RCTs]
- Predominantly colorectal surgery

Ketamine, PPSP & thoracotomy

- Duale et al, 2009, n=86
  - All had PCA, plus ketamine or saline infusion for 24 hours
  - Less morphine 24 hours, lower pain scores
  - **No differences in PPSP at 4 months**
- Hu et al, 2014, n=78
  - All had PCA, plus ketamine or saline infusion for 72 hours no difference in pain scores
  - **No difference in PPSP at 6 months**
- Tena et al, 2014, n =104
  - All had thoracic epidural, plus IV ketamine, or epidural ketamine or saline
  - lower pain scores
  - **No reduction in PPSP at 6 months**

Cochrane Review

"…results with ketamine should be viewed with caution since most of the included trials were small (that is <100 participants per treatment arm), which could lead to an **overestimation of treatment effect**"

Conclusion

- Ketamine is a non-opioid analgesic that has an effect on acute and chronic pain
- May provide pain relief in carefully selected complex pain patients
- Complements other analgesic modalities
- Safe in analgesic doses
- Do analgesic effects translate into better functional outcomes? Facilitate rehabilitation?