

Ketamine use in hospice patients before  
and after the sentinel randomised  
controlled trial of ketamine in cancer  
pain:

A single centre retrospective review

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# Overview

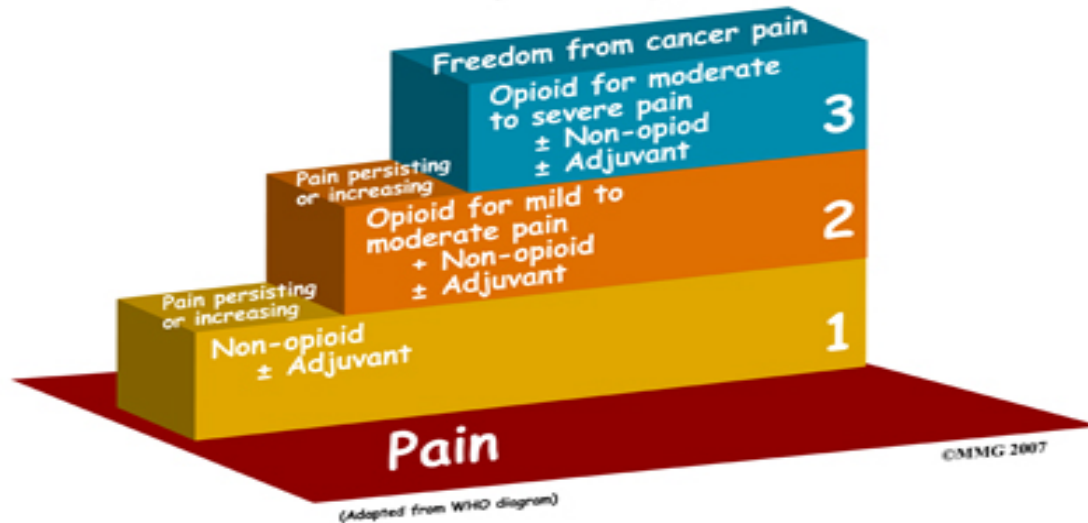
- Largest RCT of ketamine for cancer pain was published in 2012
- Results indicated no benefit from ketamine
- Practice has changed at Sacred Heart Hospice
- This retrospective review will quantify the change in ketamine use and explore the nature of the change in practice

# Background

- Pain is one of the most common and feared symptoms in advanced cancer<sup>1,2</sup>
- Pain contributes to poor quality of life<sup>2</sup>
- Investigation and management of pain and optimisation of quality of life are core skills in palliative medicine

# Pain Management

## WHO Three-Step Analgesic Ladder



- Up to 20% of patients will not be able to achieve adequate and durable pain control using this approach<sup>3</sup>

# Difficult pain control

- Pain that may be difficult to control<sup>4</sup>:
  - Significant neuropathic component
  - Incident pain, especially due to bone mets
  - High and increasing opioid doses
  - Chronic pain

# Central Sensitisation

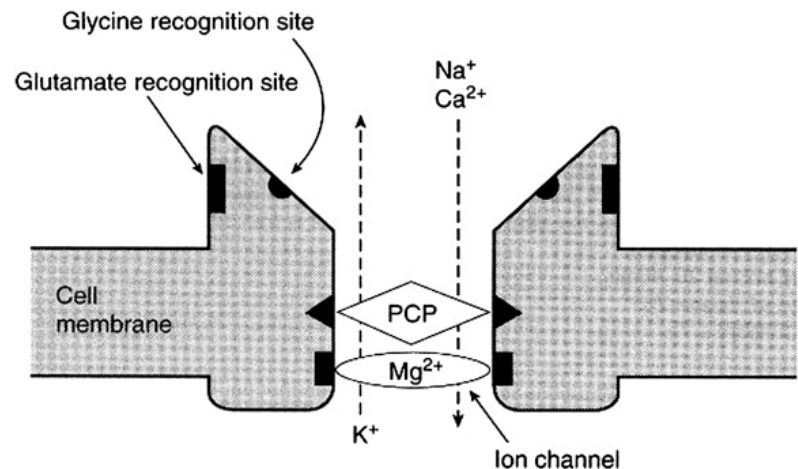
- Central sensitisation or 'wind-up'<sup>5,6</sup>
  - Repeated exposure to pain/noxious stimuli
  - Increased sensitivity of dorsal horn neurons
  - Neuronal hyperexcitability
- Same pain stimulus is felt with increasing intensity
- Hyperalgesia, allodynia, poor response to opioids

# NMDA Receptor

- NMDA receptor involved in excitatory synaptic transmission<sup>5</sup>
- Activation of NMDA receptors in spinal cord implicated in central sensitisation<sup>7</sup>
- NMDA receptor activation positive feedback loop of further activation<sup>6</sup>

# Ketamine

- Potent, non-competitive NMDA receptor antagonist<sup>6</sup>
- Dissociative anaesthetic<sup>8</sup>
- Broad range of clinical uses:
  - Acute and chronic pain
  - Complex regional pain syndrome
  - Paediatric pain management
  - Neuropathic pain
  - Depression and anxiety<sup>9</sup>
- Used in various forms<sup>8</sup>:
  - Intravenous, subcutaneous, bolus, continuous infusion, oral, intrathecal, epidural, topical





# Palliative Care

- Ketamine used in palliative care for difficult pain for a long-time
  - Little evidence guiding use
- Cochrane Database of Systematic Reviews 2012<sup>10</sup>:
  - ‘Current evidence is insufficient to assess the benefit and harms of ketamine as an adjuvant to opioids for the relief of cancer pain. More RCTs are needed’

# Hardy et al. 2012

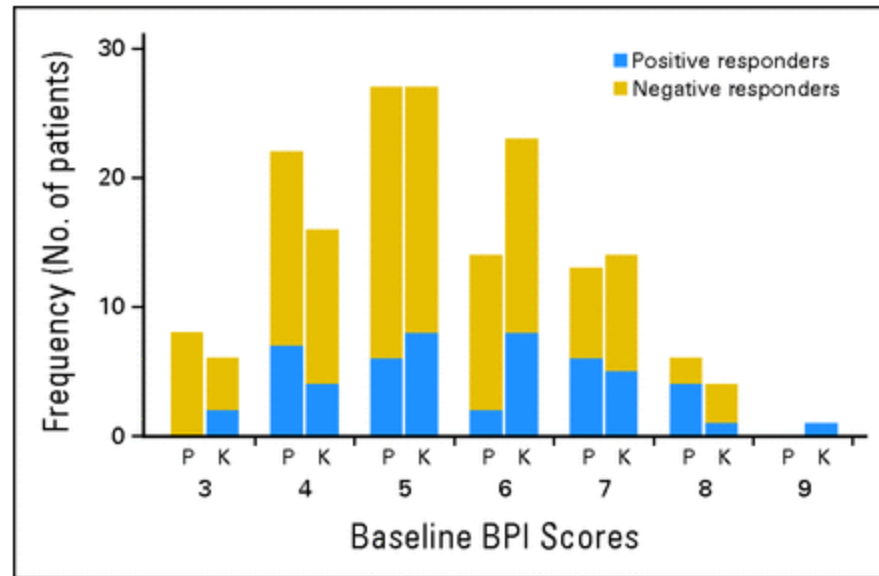
## Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain

*Janet Hardy, Stephen Quinn, Belinda Fazekas, John Plummer, Simon Eckermann, Meera Agar, Odette Spruyt, Debra Rowett, and David C. Currow*

- The largest randomised, double-blind, placebo-controlled trial of ketamine<sup>11</sup>
  - Subcutaneous ketamine vs. placebo
  - 5 day infusion
  - Chronic cancer pain of  $\geq 3$  months with BPI  $\geq 3$
  - Pain despite opioids and adjuvant analgesia
  - No change in baseline opioid dose or adjuvant analgesia in the 48 hours prior to study commencement

# Hardy et al. 2012

- 185 patients in ITT analysis
- Primary objective:
  - Pain improvement at the end of 5 days
  - Response 27% ketamine, 31% placebo (p=0.55)



# Hardy et al. 2012

- Secondary objective:
  - Adverse events
  - Almost twice as many AEs for ketamine vs. placebo

**Table 3.**  
Number of Adverse Events That Occurred During the Trial for Which the Grade Was Worse Than at Baseline

Adverse Event	Ketamine	Placebo
Cardiac arrhythmia	2	3
Cognitive disturbance	17	8
Confusion	13	9
Constipation	13	7
Dizziness	17	10
Hypertension	3	8
Hypoxia	7	8
Site irritation	31	4
Somnolence	24	17
Nausea	15	8
Vomiting	10	9
Other	20	12

# Hardy et al. 2012

- Conclusion:
  - ‘...this adequately powered RCT fails to support the current widespread practice of using subcutaneous ketamine as an adjuvant to opioids in the management of refractory pain in patients with advanced cancer.’

# Hardy et al. 2012

- Criticisms of the RCT:
  - No clinical evidence of central sensitization<sup>12</sup>
  - Moderate intensity pain<sup>13</sup>
  - Low dose of ketamine used, not weight-based<sup>14</sup>
  - Rapid up-titration
  - Only 24 hours at the maximum dose of ketamine until treatment declared failure<sup>12</sup>
- Was this the right population to use?

Ketamine and Cancer Pain: The  
Reports of My Death Have Been  
Greatly Exaggerated

# Sacred Heart Hospice

- Senior medical staff aware of Hardy et al. results March 2011
- Preliminary pharmacy database review showed a significant decrease in ketamine prescription following knowledge of RCT
- Ketamine still used in some circumstances
- How has the use of ketamine changed?



# Aims

- Quantify the change in ketamine prescribing before and after RCT
- Determine if other variables have influenced the prescription of ketamine
  - Pain type, cause, trajectory
- Determine if the use of methadone has changed among those prescribed ketamine



# Hypotheses and Rationale

- Ketamine use in all patients has significantly reduced, however it may have been used more frequently in patients with escalating pain
  - Explore if practice outside of the trial setting reflects the concerns raised regarding study population
- Methadone use may have increased among patients prescribed ketamine
  - NMDA receptor antagonist

# Study Design

- Retrospective audit of episodes of ketamine prescription at SHH for cancer-related pain
- Eligible episodes of ketamine prescription:
  - 1/3/2008 – 1/3/2014
  - SC ketamine commenced during admission or at POWH with transfer to SHH on ketamine
  - Malignancy

# Study Objectives

- Primary objective
  - Quantify the change in the prescription of ketamine before and after RCT knowledge (1/3/2008-31/3/2011 vs 1/4/2011-1/3/2014)
- Secondary objectives
  - To determine if, among those pts prescribed ketamine, there has been a change the number of pts commenced on methadone
  - To determine if there has been a change in the type of pain for which ketamine was used
  - To determine if the use of ketamine led to a change in opioid requirement

# Pain Characteristics

- Site of pain
- Type of pain
  - Nociceptive, neuropathic, mixed
- Trajectory of pain
  - Documentation of pain assessment is known to be poor<sup>15</sup>
  - Trajectory of opioid requirement prior to ketamine use as a proxy measure of pain trajectory
  - Opioid analgesia increase of  $\geq 40\%$  during 72 hours prior to ketamine commencement reflective of escalating pain

# Data Collection

- Patient case notes
- Electronic pharmacy database provided accurate history of administered medications
- Study-specific audit tool
- Opioid conversions

**Opioid Conversion Calculator**

**Patient details**

Patient name  Gender  Male  Female Date of birth  /  /  2015  Medical record number

**Current treatment**

**Step 1: Current REGULAR opioid therapy**

Opioid	Dosage	Actions
<input type="text" value="--None Selected--"/>	<input type="text"/> in 24 hours	<input type="button" value="+ Add"/>
<i>Formula: (mg/day of current opioid) x (conversion factor) = Oral Morphine (PO) Equivalent mg/day</i>		

**Step 2: Current BREAKTHROUGH opioid therapy**

Opioid	Dosage	Actions
<input type="text" value="--None Selected--"/>	<input type="text"/> in 24 hours	<input type="button" value="+ Add"/>
<i>Note: current breakthrough opioid entered to be what the patient is actually taking rather than what has been prescribed. Formula: (mg/day of current opioid) x (conversion factor) = Oral Morphine (PO) Equivalent mg/day</i>		

**New treatment**

**Step 3: Convert to final opioid**

Opioid	Dose reduction for incomplete cross-tolerance
<input type="text" value="--None Selected--"/>	<input type="text" value="none"/>

# Audit Tool - Demographics

## 14.1 Study-specific audit tool

Date of audit: \_\_\_/\_\_\_/\_\_\_\_\_

### Section 1: Patient Demographics

Patient study identification number \_\_\_\_\_

Age at admission date (yrs) \_\_\_\_\_

Sacred Heart Hospice inpatient? Yes  No

Commenced on subcutaneous ketamine during admission? Yes  No

Date of admission \_\_\_\_\_

Date of commencement of SC ketamine \_\_\_/\_\_\_/\_\_\_

Pre or post RCT? Pre  Post

Diagnosis of cancer? Yes  No

### Section 2: Characteristics of pain

- Primary cancer:
- Breast
  - Prostate
  - Lung
  - Pancreatic
  - Oesophageal
  - Gastric
  - Colorectal
  - Melanoma
  - Gynaecologic
  - Haematologic
  - Other
- 

Description of pain:

Nociceptive pain descriptive terms [1]:

- |                                    |                                   |
|------------------------------------|-----------------------------------|
| <input type="checkbox"/> Aching    | <input type="checkbox"/> Tender   |
| <input type="checkbox"/> Stabbing  | <input type="checkbox"/> Deep     |
| <input type="checkbox"/> Throbbing | <input type="checkbox"/> Sharp    |
| <input type="checkbox"/> Squeezing | <input type="checkbox"/> Cramping |
| <input type="checkbox"/> Gnawing   |                                   |

Nociceptive pain? ( $\geq 1$  of the above descriptors)  Yes  No

Not/inadequately documented

LANSS Pain Scale [23] (score for yes in brackets)

- Prickling, tingling, pins and needles (5) Score \_\_\_\_\_
- Autonomic skin changes – red, mottled, pink (5) Score \_\_\_\_\_
- Evoked pain – area abnormally sensitive to touch (3) Score \_\_\_\_\_
- Paroxysmal pain – sudden, bursting, shock-like (2) Score \_\_\_\_\_
- Abnormal skin temperature at site – hot, burning (1) Score \_\_\_\_\_
- Allodynia (5) Score \_\_\_\_\_
- Altered pin prick sensation (3) Score \_\_\_\_\_

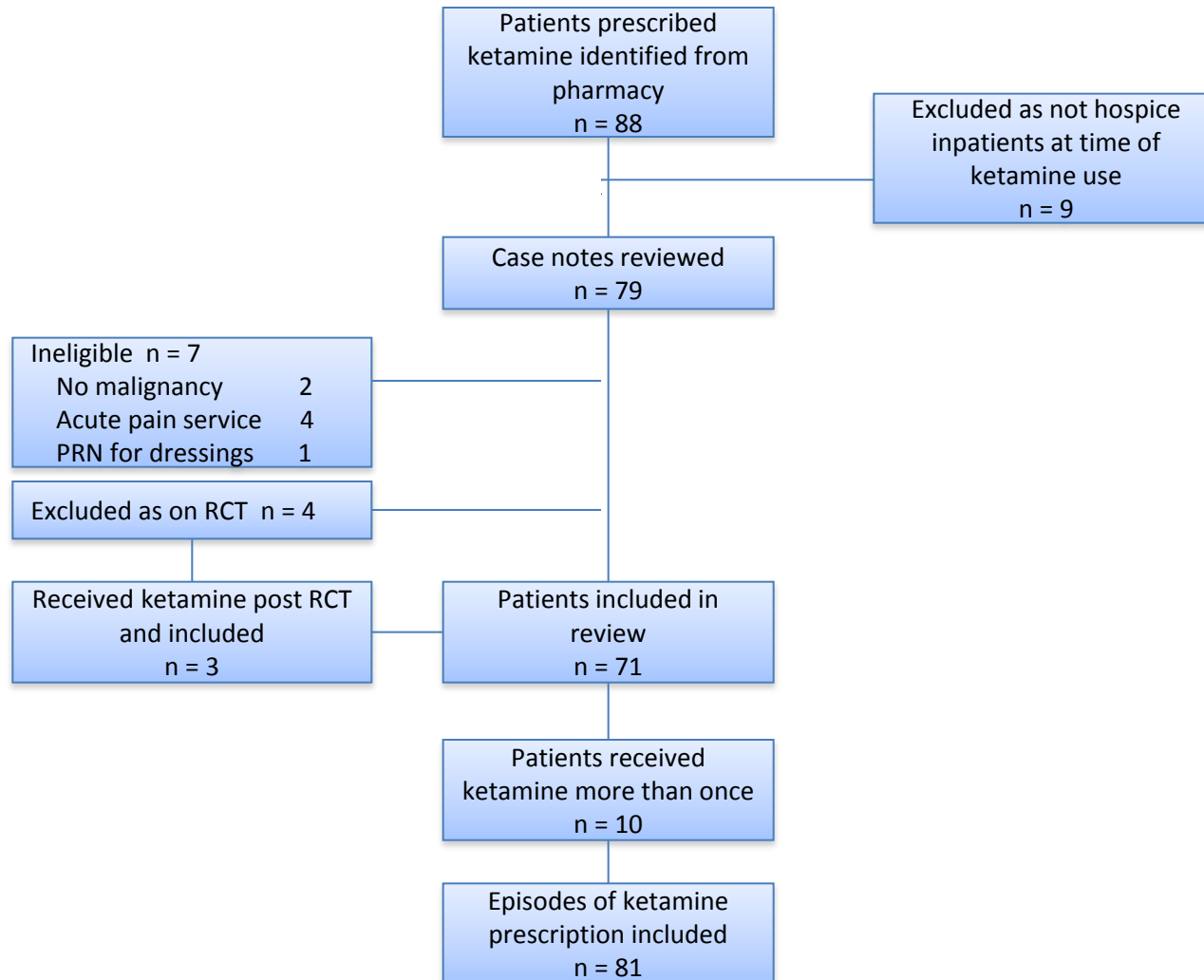
Total LANSS Pain Scale Score \_\_\_ / 24

Neuropathic pain? (score >12/24)  Yes  No

Not/inadequately documented

Mixed pain? (Yes for both nociceptive and neuropathic pain)  Yes  No

# Episodes of Ketamine Use



# Primary Objective

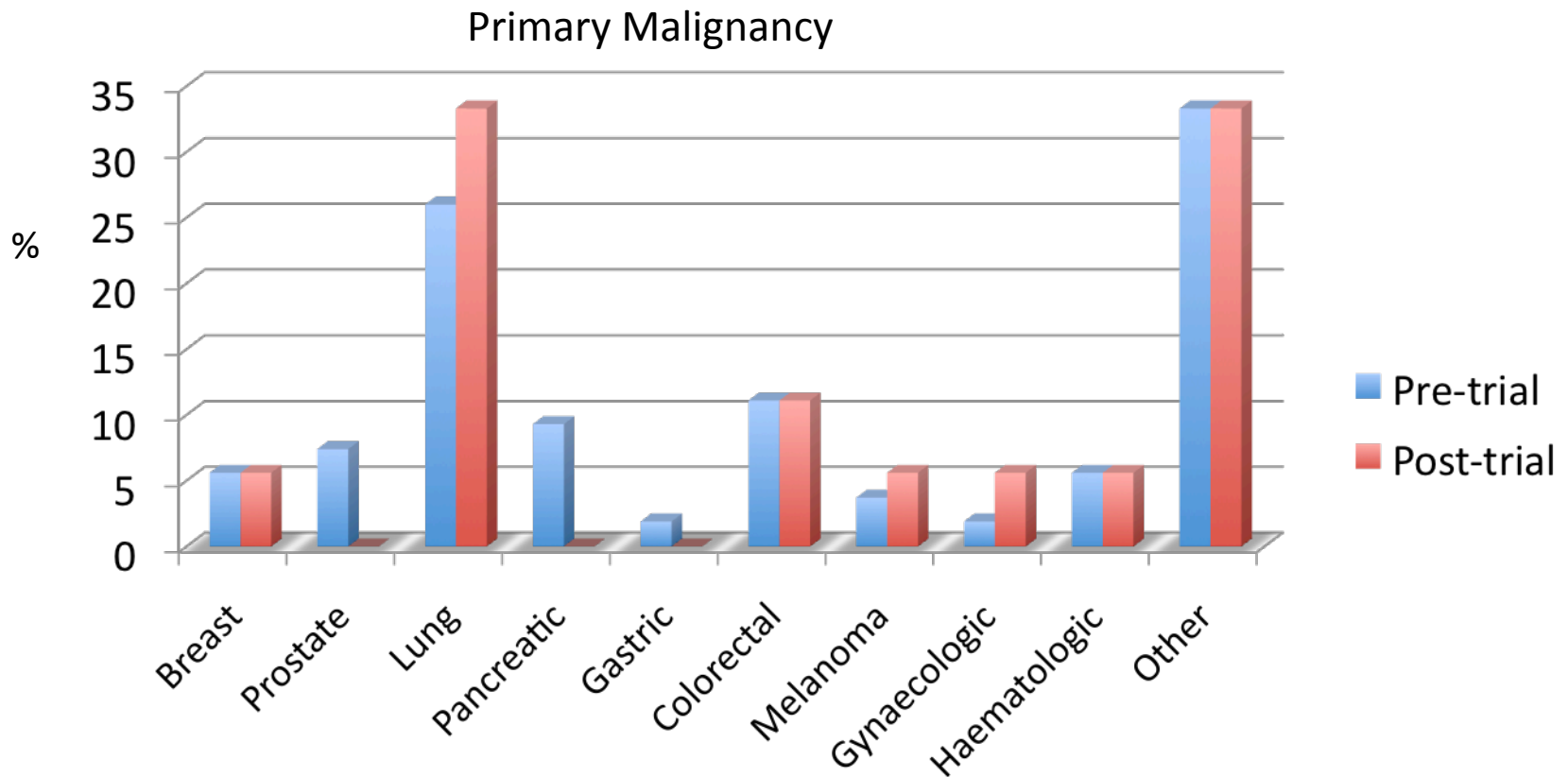
	1/3/2008-31/3/2011	1/4/2011-1/3/2014
Occasions of ketamine use	60	21
% of cancer admissions	3.28%	1.36%

58% relative reduction in ketamine use for cancer pain among cancer-related admissions to Sacred Heart Hospice following knowledge of the RCT results ( $p < 0.005$ )



# Demographics

	1/3/2008-31/3/2011	1/4/2011-1/3/2014
Average age (St Dev)	58.9 (14.9)	59.4 (13.55)
Age range	26-87	36-81

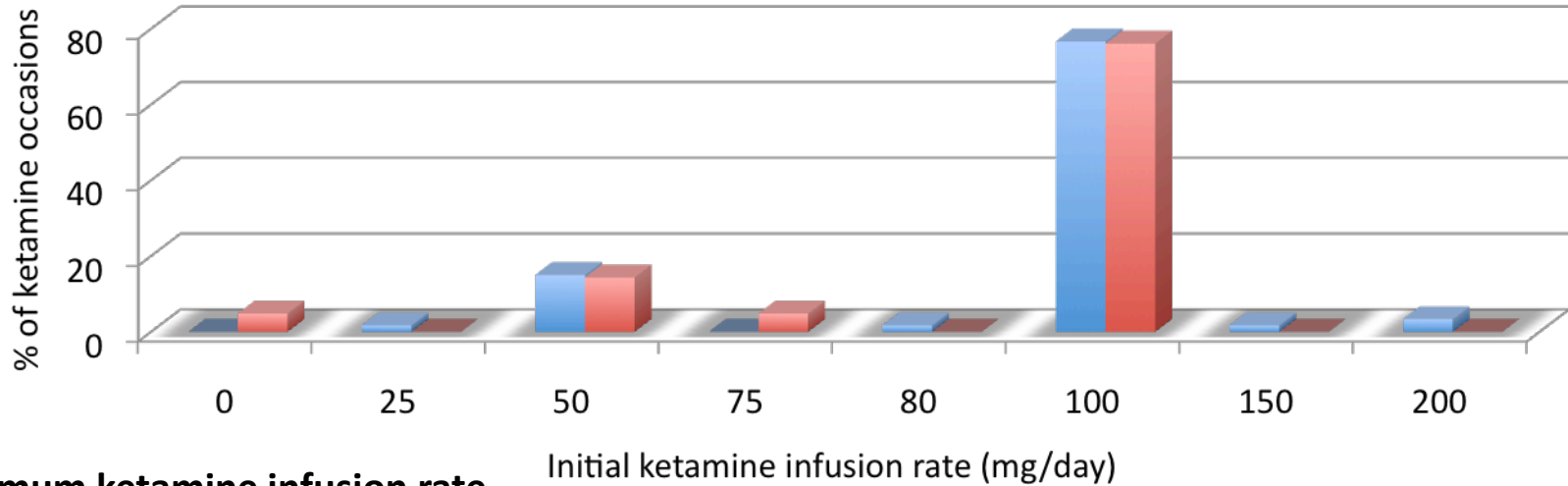


# Ketamine

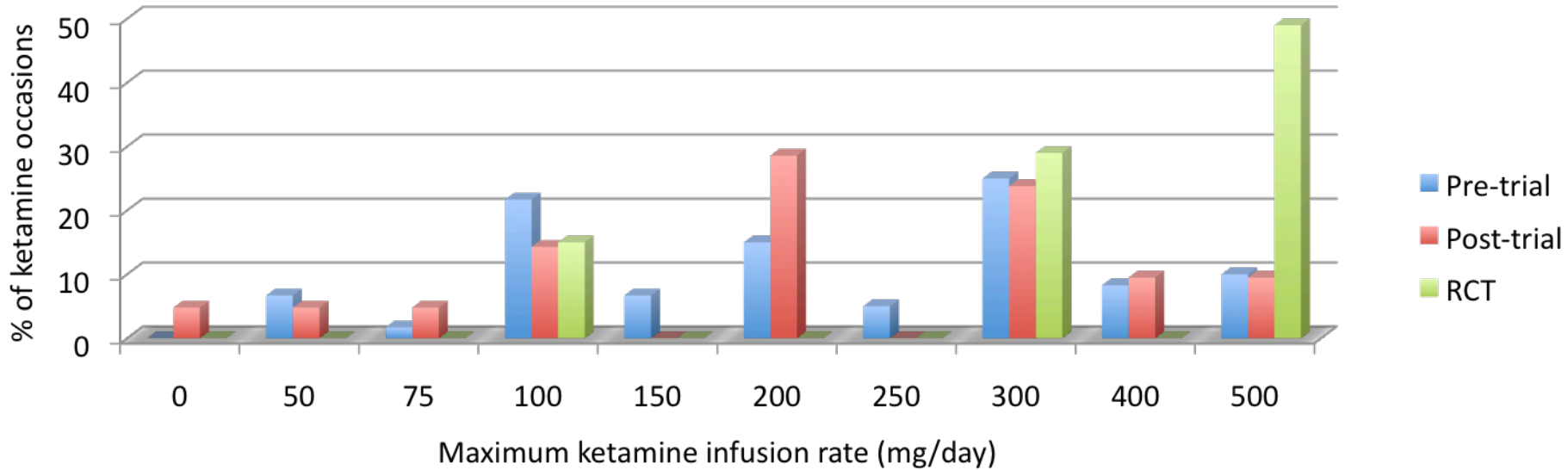
	Pre-trial	Post-trial
Loading dose	51/60 (85%)	19/21 (90%)
Adverse event post loading dose	2/51 (4%)	1/19 (5%)
No loading dose	9/60 (15%)	2/21 (10%)
Average duration of infusion (days)	12.26	12.14
Infusion duration range (days)	0.5-84	0-89

# Ketamine

## Initial ketamine infusion rate



## Maximum ketamine infusion rate



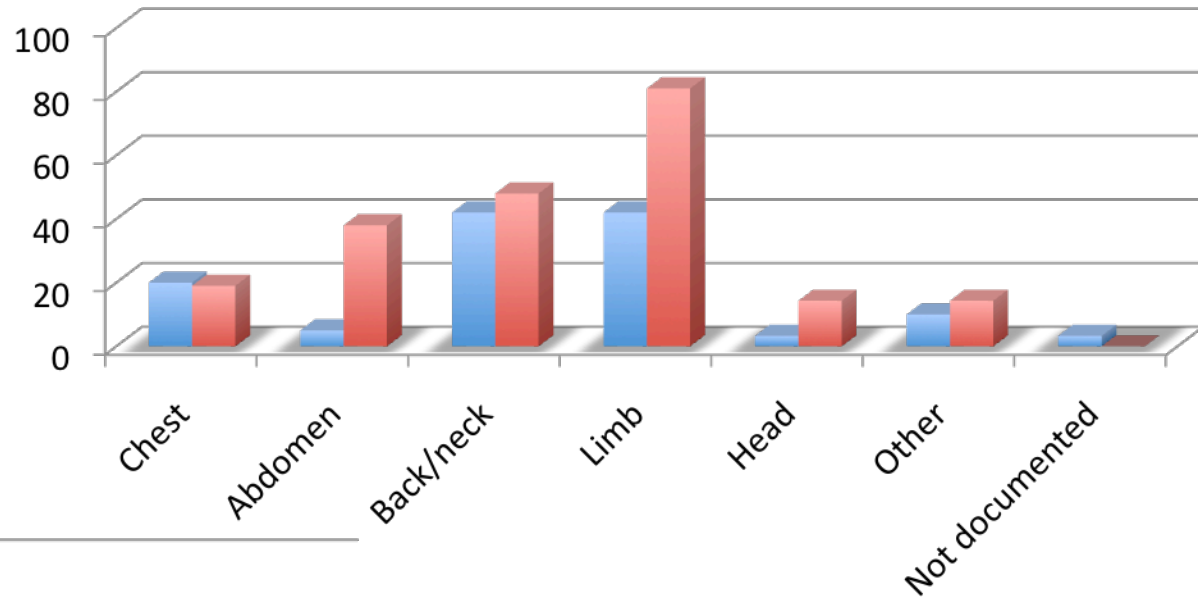
# Methadone Use

	Pre-trial	Post-trial
Methadone commenced before ketamine used	23	11
Methadone commenced after ketamine use	5	2
Unclear timing of methadone	1	
Mean no. of opioids used	2.5	2.8

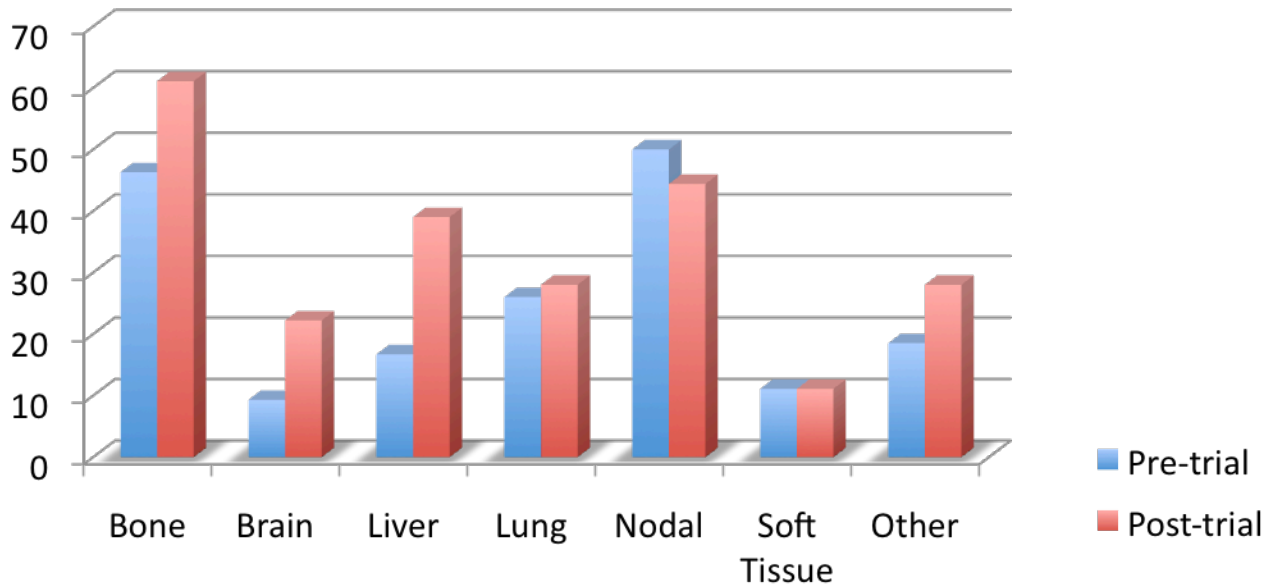
No significant difference in the use of methadone overall (49% vs 62%) or the use of methadone following ketamine infusion 8.3% vs 9.5%

# Pain Characteristics

Sites of Pain



Sites of Metastatic Disease



# Pain Type

	Pre-Trial	Post-Trial
<b>Documented Pain Type</b>		
Nociceptive	0	0
Neuropathic	28%	19%
Mixed	5%	9.5%
Not documented	65%	67%
<b>Pain Descriptors</b>		
Nociceptive Descriptors	38.3%	14.3%
Not documented	60%	81%
Neuropathic descriptors (LANSS)	3.3%	0
Not documented	95%	95%
Mixed	3.3%	0
Not documented	95%	95%

# Pain Trajectory

	Pre-trial	Post-trial
Escalating	17	6
Stable	33	12
Unknown	10	3

Among the incidents of ketamine use where the opioid trajectory was known, there was no significant difference in the incidence of escalating pain before and after the RCT

34% pre-trial vs 33% post-trial ( $p=0.73$ )

# Opioid requirement

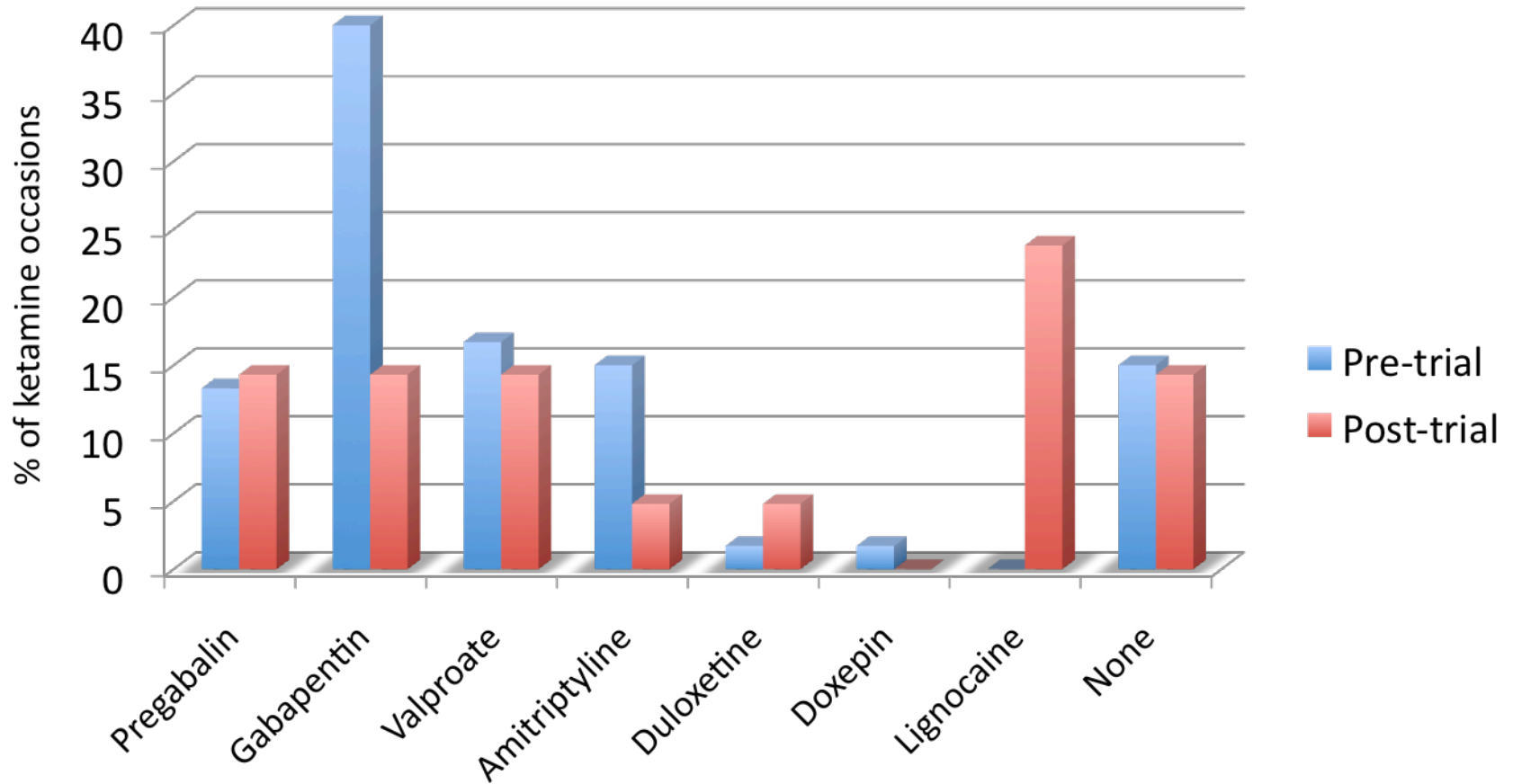
- Difference in opioid requirement pre and post ketamine was studied as a measure of ketamine efficacy
- Wide variation in the difference in opioid requirement
- No trend demonstrated in either time period
- Examination limited due to deaths and discharges
- 1 patient in each of the pre- and post-trial cohorts used no opioid analgesia prior to ketamine



# Deaths

- A significant proportion of patients died while receiving ketamine infusion in both cohorts:
  - 26/60 (43%) prior to the trial
  - 12/21 (57%) after the trial
- In the RCT, no deaths were recorded
  - Among the 181 patients who received trial agent, 12 patients withdrew due to clinical deterioration (6.6%)

# Adjuvant Analgesia



# Palliative Care Practice Survey

- Australian palliative care practitioners surveyed following the RCT<sup>16</sup>
  - 92% confirmed knowledge of the trial results
  - 63% reported a reduction in their use of ketamine
- Patient selection for ketamine was a predominant theme in survey responses
  - 87% of those reporting a decrease in ketamine use stated they are more selective in the patients for which they use ketamine
  - 71% of those who have not changed practice believe ketamine to have a role in specific patients

# Refractory Pain

- Affects up to 20% of patients with advanced malignancy, however evidence-based therapeutic options are limited<sup>17</sup>
- Alternatives to ketamine identified by survey respondents<sup>16</sup>
  - Methadone, opioid switching, lignocaine
- Evidence for methadone, opioid switching includes case series, retrospective review, uncontrolled studies, expert opinion<sup>17</sup>
- Evidence for lignocaine mostly derived from non-malignant pain literature<sup>18</sup>

# End of Life Care

- Ketamine has been used differently to the RCT
  - Slower uptitration, longer infusion duration
  - Survey respondents also reported different schedules<sup>16</sup>
- Significant numbers of patients died while still receiving ketamine both before and after RCT
- Up to 80% of patients will suffer with delirium during their final days<sup>19</sup>
- Given the significantly increased risk of psychotomimetic side effects associated with ketamine in the RCT, what does this mean for patients at the end of life?

# Conclusion

- We have demonstrated a change in practice as a result of new evidence
- The issue of patient selection for ketamine remains unclear
- The use of opioid trajectory as a proxy measure of escalating pain reflective of sensitization was pragmatic, but limited
  - Broad differential for increasing opioid requirement
  - Likely to have missed some patients with unstable pain

# Conclusion

- Identification of the patient population and pain to examine is a key challenge
- The use of appropriate, effective therapies with well understood side effect profiles is important in palliative care
  - Vulnerable to increased symptom burden from meds
  - Limited time to await efficacious treatments

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