Ketamine
Guildford Advanced Course

Dr Barry Laird
Senior Lecturer in Palliative Medicine
Institute of Genetics and Molecular Medicine
University of Edinburgh

Consultant in Palliative Medicine
St Columba’s Hospice & Edinburgh Cancer Centre
1. **By the clock**
   Cancer pain is continuous - use regular dose intervals (*not* prn)

2. **By the 'ladder'**

   **Step 1**
   - Non-opioid, e.g. NSAID, paracetamol, ± adjuvant analgesic
   - Pain persisting or increasing

   **Step 2**
   - Opioid for mild to moderate pain, e.g. codeine, ± non-opioid, ± adjuvant analgesic
   - Pain persisting or increasing

   **Step 3**
   - Opioid for moderate to severe pain, e.g. morphine, ± non-opioid ± adjuvant analgesic

   **Pain Controlled**
   - Adjuvant analgesic drugs may be added at any step of the ladder

The ladder has no "top rung" as there is no maximum dose for strong opioids. If pain is still a problem with high doses of morphine (e.g. >300mg/24 hours), or severe side effects, reconsider the cause of pain, e.g. bone pain may be better helped by NSAIDs, and/or seek specialist advice.

3. **By the mouth**
   The oral route is preferred for all steps of the analgesic 'ladder'.
Maintenance of therapeutic drug levels

- **Range**
  - **Plasma level causing toxicity**
  - **Toxicity**
  - **Analgesia**

- **Patient in pain**
- **Bolus**
- **Bolus (loading dose)**
- **Start continuous infusion or around the clock regimen**
Challenge

• Morphine and other opioids are key in moderate to severe cancer pain (and many non-malignant pains)

HOWEVER

• Side-effect profile can limit dose titration
• Effectiveness can be attenuated by changes in peripheral and central pain pathways
Adjuvants in Neuropathic Pain: a ladder

1. Amitriptyline
2. Gabapentin/Pregabalin
Addition of 1+2
(Based on nnt’s)
- Duloxetine
- Venlafaxine
- Carbamazepine
- Lidocaine patches

- Ketamine
Solutions

- Minimize opioid side-effects through improved assessment and use of adjuvant analgesics particularly in neuropathic, bone pain or mixture of such pains

- Attenuate/reverse changes in peripheral and central pain pathways with appropriate adjuvant analgesics
They’ve cut the phone line – paradox NP

- Plastic nerve system
- Not hard wired
- Adapts to change
- Damaged nerve
- Neuroma formation

- Spontaneous discharge of neuroma
- Discharge to normal stimuli
- Increased ectopic firing
- “sensitised nerve”

Decreased pain threshold
Increase pain response
Sensitive to non noxious stimuli
Ketamine

- $\text{C}_{13}\text{H}_{16}\text{ClNO}$
- MW 237.725 g/mol
- Bioavail 93% IM, 17% oral
- Metabolised liver
- half life 2.5-3 hours.
- Excretion: renal (>90%), urine
Mechanisms of Action (1) - NMDA

Active in pain states releasing glutamate
Activation contributes to wind up – resulting in central sensitisation and opioid tolerance

NMDA interference
- Opioid synergy
- ↑ opioid responsiveness
- ↓ opioid requirements

Compounds influencing NMDA
1) Competitive antagonists
2) Open channel blockers (Mg opened)
3) Non-competitive antagonists

Ketamine – low affinity open-channel blocker NR2B
Only blocks NMDA when open for a prolonged period
Minimal effect when NMDA only transiently open (usual)
Mechanisms of Action (2) - Opioids

- Also acts directly on delta opioid receptor
- Acts to augment mu-opioid receptor function
- Modifies responsiveness to opioid receptors - not influenced by naloxone – primary MOA not opioid receptors
Mechanisms of Action (3) - Inhibition

Descending inhibition of pain (endogenous pain modulation) – key component of pain processing

Conditioned Pain Modulation (CPM) – i.e. central inhibition via other stimuli

CPM impaired in chronic pain states

Inability to start descending inhibition

Hypothesis: ketamine enhances CPM
REVIEW

Ketamine – More mechanisms of action than just NMDA blockade

Jamie Sleigh, Martyn Harvey, Logan Voss, Bill Denny

Channel effects
- ↓ NMDA
- ↓ HCN1
- ↓ nACh
- ↓ L-type Ca

Neuromodulation effects
- ↑ Glutamate
- ↑ Noradrenaline
- ↑ Dopamine
- ↑ Cortical ACh
- ↓ Pontine ACh
- ↓ Opioids & ERK1/2
- ↓ mGluR
- ↑ Neurosteroids
- ↓ NOX
- ↑ AMPAR insertion
- ↑ NMDAR1
- phosphorylation and expression

Gene expression
- ↑ Immediate Early Genes
- ↑ GFAP expression
- ↑ BDNF
- ↑ mTOR
- ↑ Rgs4

Cellular Effects
- Synaptic homeostasis
- Apoptosis
Pharmacokinetics

- Water and lipid soluble
- Metabolised by liver to norketamine
- Norketamine greater analgesic potency than ketamine
- Norketamine undergoes hydroxylation and conjugation before renal excretion
- SE due to effects at other receptors
Evidence base – ketamine
(or why do we do what we do with ketamine)
(Post op, Neuropathic pain, Cancer pain)
Is ketamine beneficial in ischaemic pain?
A single infusion of IV ketamine improves pain relief in patients with critical limb ischaemia:
Mitchell AC, Fallon MT. Pain2002;97:275-281

- Ischaemic pain mimics neuropathic pain (Similar eg allodynia, hyperpathia and hyperalgesia)
- Basic scientific suggests NMDA mediated
- n=35
- Single infusion 0.6mg kg infusion
- Haloperidol used, improvement lasted for 5 days
Is ketamine a useful adjuvant in cancer related pain?

Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. Cochrane database of systemic reviews.

- 4 studies – two poor methodological quality
- RDBPC crossover double dose study
- Ketamine reduced pain at both doses
- SE increase as dose increases

Mercadante et al; JPSM 2000;20(4):246-252
Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subcutaneous Ketamine in the Management of Cancer Pain

Janet Hardy, 1
Brisbane, Qld

PATIENTS AND METHODS

Eligibility and Enrollment

Participants were recruited from 10 palliative care services in a range of metropolitan settings across Australia.8 Eligible patients were in-patients aged 18 years or older. All met the definition of refractory chronic pain secondary to cancer or its treatment9 with a Brief Pain Inventory (BPI)10 average pain score of ≥ 3 despite ongoing treatment with opioids and coanalgesics at predefined dose levels (Appendix Table A1, online only). Patients were excluded if they had received ketamine for chronic pain within 6 months, radiotherapy to a site of pain within 2 weeks, any other procedure or therapy likely to affect pain during the trial period, or comorbidities contraindicating the use of ketamine.11 All participants were formally assessed for cognitive ability to undertake trial requirements (Fig 1).

Interventions

No change in baseline opioid dose or coanalgesia was allowed in the 48 hours before study commencement. No increase in baseline opioid dose was allowed during the study, but participants had access to breakthrough analgesia. Opioid dose reduction was allowed for pain response or opioid toxicity. Total daily opioid dose and number of breakthrough analgesic doses were recorded.

Subcutaneous infusions of placebo (normal saline) or ketamine at three dose levels (100, 300, or 500 mg) were prepared by diluting ketamine hydrochloride 200 mg/2 mL in normal saline to a set volume. Participants received either ketamine or placebo in a 5-day schedule, starting at the first dose level (100 mg/24 hours; Fig 2). Pain and toxicity assessments were undertaken every 24 hours by trained research staff. Least, average, and worst pain over the preceding 24 hours were assessed by using the BPI. If 80% of study drug had been delivered, and average pain improved by ≥ 2 BPI units with no more than four breakthrough doses, the dose remained the same. If not, the dose was increased to the next level. Any psychomimetic toxicity was treated promptly with haloperidol or midazolam at specified doses. Dose reduction to the previous level was allowed in the case of unacceptable toxicity. Study drug was discontinued before 5 days if toxicity was intolerable or if there was no response after 24 hours at 500 mg.

Randomization and Masking

Each site pharmacy used randomization tables from an independent central registry. Stratification was by pain type (neuropathic or nociceptive), according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale.12 Randomization was double blinded, allocated by blocks of four in a 1:1 ratio for each strata by site. All nonpharmacy study staff, treating clinicians, investigators, and participants were unaware of treatment allocation until completion of all data collection and analysis.

Definition of a Clinically Relevant Improvement in Pain

A clinically relevant improvement in pain was defined as a reduction in BPI average pain score by ≥ 2 points from baseline in the absence of more than four breakthrough doses of analgesia over the previous 24 hours.13

Completion

Participants were defined as having completed the study if they had received study drug for 5 days, or received 24 hours of study drug at maximum
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketamine (n = 93)</th>
<th>Placebo (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Age, years</td>
<td>63.0</td>
<td>13.7</td>
</tr>
<tr>
<td>Male sex</td>
<td>50</td>
<td>55.0</td>
</tr>
<tr>
<td>Site of cancer diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>22</td>
<td>24.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>13</td>
<td>14.3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>8</td>
<td>8.8</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>8</td>
<td>8.8</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>6.6</td>
</tr>
<tr>
<td>Bone/soft tissue</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5</td>
<td>5.5</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>28.6</td>
</tr>
<tr>
<td>Performance status (AKPS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>50-60</td>
<td></td>
</tr>
<tr>
<td>Background opioid dose OME, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>160-480</td>
<td></td>
</tr>
<tr>
<td>BPI pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>5.43</td>
<td>1.3</td>
</tr>
<tr>
<td>Worst</td>
<td>8.08</td>
<td>1.5</td>
</tr>
<tr>
<td>Least</td>
<td>2.47</td>
<td>1.7</td>
</tr>
<tr>
<td>LANSS score ≥ 12</td>
<td>28</td>
<td>30.1</td>
</tr>
<tr>
<td>CADSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>55</td>
<td>59.8</td>
</tr>
<tr>
<td>1-2</td>
<td>19</td>
<td>20.7</td>
</tr>
<tr>
<td>3-8</td>
<td>12</td>
<td>13.0</td>
</tr>
<tr>
<td>9+</td>
<td>6</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Fig 4. Mean pain scores over time (adjusted for arm, time, arm × time, ln(time), background opioid dose, age, sex, and pain type [n = 181]). P values are differences between arms at study end. Error bars represent 95% CIs. BPI, Brief Pain Inventory.
### Table 2. Maximum Dose Received by Participants in Each Arm

<table>
<thead>
<tr>
<th>Ketamine/Placebo Dose (mg)*</th>
<th>No. of Patients Who Received Ketamine</th>
<th>No. of Patients Who Received Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>6†</td>
<td>7†</td>
</tr>
<tr>
<td>100</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>300</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>500</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

*Participants were required to complete that dose level.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Site irritation</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

In 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.
Ketamine in the Management of Cancer Pain

TO THE EDITOR: I read the excellent article written by Hardy et al. in *Journal of Clinical Oncology*. Although the methodology and study design was of high scientific quality, there were several points that were not discussed in this interesting article.

As Hardy et al. pointed out, we have little evidence from controlled studies on ketamine use in patients with cancer with pain. However, when such a powerful drug is used, it is important to titrate the dose in a careful way. In this study, the presented schedule of dose increments was conducted during 5 days. The scheme was as follows: 100, 300, and 500 mg per day in a continuous subcutaneous infusion. Because the study duration was only 5 days, this scheme seemed to be an aggressive approach, especially when the daily dose was increased from 100 to 300 mg (by 300%).

Because the careful titration of opioid analgesics is recommended, it seems that more-careful ketamine dose increments (e.g., from 50 to 100, 150, 200, 250, and 300 mg) may be associated with less-adverse events. This effect might also be the case when the dose is increased from 300 to 500 mg.

Another interesting point in the study by Hardy et al. was that patients recruited at baseline experienced pain of moderate intensity (5.43 ± 1.3 and 5.21 ± 1.4 in the ketamine and placebo arms, respectively) according to the Brief Pain Inventory pain-on-average item. All patients had been treated at entry with high opioid doses (median oral morphine equivalents) of 300 mg (range, 160 to 480 mg) and 410 mg (range, 258 to 700 mg) in the ketamine and placebo arms, respectively. One of the entry criteria was that the average pain score was 3 or more on the Brief Pain Inventory. However, in clinical practice, a score of 3 or 4 may be acceptable for many patients, especially those suffering from neuropathic pain who usually experience severe pain (score > 6). High opioid doses might have contributed to the adverse effects observed.

From our experience, the indication on the concurrent use of opioids and ketamine could be severe neuropathic pain intensity (Numerical Rating Scale ≥ 7) that does not respond to opioids and adjuvant analgesics. The starting dose of ketamine should be low and titrated carefully to achieve satisfactory analgesia and acceptable adverse effects; then, the opioid dose may be reduced. Patients should be closely monitored at specialist in-patient units. Ketamine may also be used for painful hygienic procedures or for changing dressings in patients after major burns.

Mechanisms of ketamine analgesia include N-methyl-d-aspartate-receptor blockade, decrease of central sensitization, reduction of hyperalgesia, and reverse of opioid tolerance. Results of controlled studies have suggested a lack of efficacy and increased toxicity when ketamine and opioids were used concurrently. It seems that we need additional controlled studies with longer follow-up that could confirm or challenge these results and look for alternatives. One possibility is the use of methadone that combines the effects of the opioid agonist and N-methyl-d-aspartate-receptor antagonist. Uncontrolled reports demonstrated the efficacy and safety of small methadone doses added to other opioids, which may reduce risks associated with complex pharmacokinetics and appropriate dosing. Meanwhile, we should be grateful to Hardy et al. for conducting such a challenging study, and we should undertake additional controlled trials to find the best approach for patients with cancer with severe pain.

Wojciech Leppert
Poznan University of Medical Sciences, Poznan, Poland

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES


DOI: 10.1200/JCO.2012.47.5939; published online ahead of print at www.jco.org on February 19, 2013
Ketamine and Cancer Pain: The Reports of My Death Have Been Greatly Exaggerated

To the Editor: We are writing in response to the article by Hardy et al., entitled, "Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Toxicity of Subanesthetic Ketamine in the Management of Cancer Pain." The authors are to be congratulated on successfully completing a placebo-controlled, randomized controlled trial in 185 patients receiving palliative care—no mean feat.

However, we question whether the authors’ sweeping conclusion that "Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard cosolagies in cancer pain" is appropriate, when considering the way that many palliative medicine and pain medicine specialists use ketamine. Many of us have been using so-called "buno" ketamine for the last decade. Ketamine was used in this manner in two strictly controlled, open-label prospective audits, which showed 29 of 43 and 22 of 44 positive responses, respectively. There is an obvious potential for observer bias and placebo responses in open-label trials; however, the differences between the results of Hardy et al. and our own results may also be explained by differences in three factors: patient selection, the duration of ketamine use before it is deemed a treatment failure, and the management of psychomimetic adverse effects (AEs).

Ketamine is a so-called "dirty" drug, but its major postulated action in pain control is as an N-methyl-D-aspartate antagonist. N-methyl-D-aspartate activation contributes to central sensitization, which occurs with ongoing nociceptive input from inflammation or injury and also seems to be one of the mechanisms that is associated with neuropathic pain states. The clinical manifestations of central sensitization include ongoing and escalating pain, hyperalgesia, allodynia, and relative nonresponsiveness to opioids. It is indeed in patients who show these characteristics that we particularly advocate using ketamine, rather than in patients like those in the study by Hardy et al., who had " refractory chronic pain...typically for longer than 3 months" as per the protocol of Hardy et al. Once established, central sensitization, together with the other neurophysiologic changes that are associated with pain chronicity, may not be reversible, and chronicity is recognized as a poor prognostic factor for achieving subsequent good pain control. Interestingly, there is increasing evidence that supports ketamine having an anti-inflammatory action at multiple levels. Thus, its analgesic action may in part be a result of reducing the levels of pronociceptive cytokines such as interleukin-1β in the dorsal horn of the spinal cord. Additionally, pain mechanisms rather than pain etiology are increasingly being recognized as important in identifying the likely efficacy of any analgesic medication.

Hardy et al. categorized the patients that they studied only as nociceptive or neuropathic. In our research, including our two audits, we found that somatic nociceptive pain achieves the best response—specifically, positive responses in 5 of 5 patients and 3 of 5 patients with mucositis pain, and 8 of 9 patients and 6 of 11 patients with bony metastases pain, respectively. Thus, perhaps we and Hardy et al. were studying dissimilar patient populations as defined by both chronicity and dominant pain mechanism?

Hardy et al. state that they used their dose-escalation protocol; however, they deemed treatment to have failed if there was "no clinically relevant pain response" after 24 hours at the maximum dose of 500 mg over 24 hours, rather than after 3 days, as in our protocol. Additionally, we have learned from our experience over the last 10 years, and remembering that these patients have few other options, we now on occasion continue ketamine for up to 1 week before judging it to be ineffective. By ceasing ketamine after 24 hours if there was no meaningful response to ketamine at a dose of 500 mg administered over 24 hours, did the trial by Hardy et al. miss a number of potential responders?

We concur with Hardy et al. on the potential for psychomimetic AEs (which seem to increase with increasing age and ketamine dose) and acknowledge that these would likely constitute an obstacle to long-term and/or outpatient treatment. The majority of AEs are National Cancer Institute grade 1 or 2, although in our second audit we saw 11 National Cancer Institute grade 3 or 4 neurologic AEs in 44 patients (and we now use prophylactic low-dose haloperidol or midazolam concurrently).

However, no patient in either audit who had achieved a good response elected to cease ketamine early (and we specifically offered this option); that is, the patients seemed prepared to trade short-term AEs for long-term gain. Conversely, Hardy et al., because of the constraints imposed by their protocol, withdrew 22 of 93 patients because of toxicity. Again, how many of these patients were potential responders?

In summary, we contend that the conclusions from the article by Hardy et al. are valid only under the specific conditions of their protocol and do not necessarily apply to how we, and many others, use ketamine. We also suggest that the large body of randomly anecdotally collected evidence should not be dismissed without further investigation.

Kate Jackson and Michael Franco
Southern Health and Monash University, Clayton, Victoria, Australia

Lee Roy William
Southern Health and Monash University, Clayton; Eastern Health, Monaroondah, Victoria, Australia

Peter Poone
Southern Health and Monash University, Clayton; and Eastern Palliative Care, Nunawading, Victoria, Australia

Maria Fissale
Werribee Mercy Health, Werribee, and Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

David Kemner
Eastern Health, Box Hill, Victoria, Australia

David Brunley and Greg Mewett
Grampians Regional Palliative Care Team, Balairst, Victoria, Australia

Michael Ashby
Royal Hobart Hospital and Southern Tasmania Area Health Service, Hobart, Tasmania, Australia
<table>
<thead>
<tr>
<th>Hardy et al</th>
<th>Fallon et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBRCT</td>
<td>DBRCT</td>
</tr>
<tr>
<td>Placebo Controlled</td>
<td>Placebo Controlled</td>
</tr>
<tr>
<td>Inpatients</td>
<td>In or out-patients</td>
</tr>
<tr>
<td>Titration of IMP</td>
<td>Titration of IMP</td>
</tr>
<tr>
<td>Subcutaneous administration</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Refractory cancer pain</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Patients with active cancer</td>
<td>May have active cancer (or cured)</td>
</tr>
<tr>
<td>On opioids</td>
<td>May be on opioids</td>
</tr>
</tbody>
</table>
Participants

Eligible patients met the following criteria: ≥18 years of age; a diagnosis of current or previous cancer; neuropathic pain (defined as a Short Form-McGill Pain Questionnaire-Sensory Component [SF-MPQ-SC] score >5, together with a positive score on the Leeds Assessment of Neuropathic Symptoms and Signs [LANSS])\(^{(21, 22)}\); pain severity ≥4 on a 0–10 Numerical Rating Scale (NRS); received or offered a trial of ≥1 adjuvant analgesic, e.g. tricyclic antidepressant, anti-epileptic. Patients were excluded if ketamine was contra-indicated, e.g. psychotic illness, or they had recently received a treatment that could impact on the pain within the duration of the trial, e.g. radiotherapy, nerve block.

To ensure consistent assessment throughout the trial, the neuropathic pain was designated the ‘index pain’. Analgesic use was also recorded; the dose of an opioid could be adjusted, but not that of an adjuvant analgesic.
Endpoints

Primary
Improvement in NP – time to treatment failure

Secondary
Pain (AP, WP), LANSS, Mood, Distress, QoL, AE
Study Design

Run in phase / Titration phase. Assessment Phase
So where does this leave us?
Precision in Palliative Medicine

- Right drug, right patient, right time
- Ketamine still used clinically
- Role in patients with central sensitisation