Ketamine – or the power of placebo

JR Hardy

Mater Research – University Qld

Centre for Palliative Care Research and Education

Refractory cancer pain

-Pain related to cancer or its treatment

-At least 3 months duration

-Incomplete response to standard therapy (opioids, co-analgesics)

-Terminology: difficult pain, persistent, intractable, opioid nonresponsive

-10-20% of cancer patients

Refractory cancer pain

-Young age

-Neuropathic pain vs nociceptive

-Incident pain

-Psychological distress

-Previous opioid use/addiction

-High tolerance

-Impaired cognition

Refractory cancer pain

Worse pain prognosis

-mixed pain type

-high pain severity

-daily opioid use

-long term opioid use

-poor emotional wellbeing

Options for management

Opioids

- parenteral route

- opioid rotation

- opioids in combination

- methadone, buprenorphine

Non-Opioid analgesics and co-analgesics

- paracetamo/NSAIDs

- antidepressants

- anticonvulsants

Options for management

Cannabinoids

Lignocaine

Corticosteroids

N-methyl-D-aspartate (NMDA) receptor anatagonists

Afsharimani et al, Support Care Cance, 2015


Special

Ketamine

-dissociative anaesthetic agent,

-analgesic properties at sub-anaesthetic doses

-most potent NMDA-receptor-channel blocker available for clinical use

-also has opioid-like and anti-inflammatory effects

-interactions with other Ca, K and Na channels

-plus cholinergic, dopaminergic and noradrenergic transmission

-action on descending inhibitory pathways

-resultant changes in gene expression, protein regulation could explain ongoing benefit post discontinuation of ketamine

Wilcock et al :JPSM, Therapeutic review August 2015

Recommendations for use

No standard:

- *Dose (10mg test – 3.6g/24 hours)*
- *Route (iv, subcut, oral, intrathecal)*
- *Regimen (stat dose, continuous infusion)*
- *Schedule (“burst”, monthly, 3 monthly, as required)*

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Evidence of benefit in chronic cancer pain

- multiple anecdotal and uncontrolled studies showing benefit (Level 4)
- Cochrane review : 28/32 reports described improved analgesia
- wide range of dose and route
- 16 of 32 studies not included reported dramatic improvement in analgesia
- 2 studies met criteria for Cochrane review, both showing analgesic benefit (30 pts)

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Cochrane conclusion

- “Current evidence is insufficient to assess the benefits and harms of ketamine when used as an adjunct to morphine”
- update 2007, no new evidence
- “more research needed”

A randomised, double blind, placebo controlled study of subcutaneous ketamine in the management of cancer pain

Prof Janet Hardy - on behalf of the Palliative Care Clinical Studies Collaborative (PaCCSC)

Funded by the Australian Government Department of Health and Ageing under the National Palliative Care Strategy

JCO 2012;30 (29):3611-7

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A randomised, double blind, placebo controlled study of subcutaneous ketamine in the management of cancer pain

- Aim : to assess whether subcutaneous ketamine, dose escalated over 5 days, was more effective than placebo in the management of cancer pain

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Inclusion criteria

- hospital in-patients with uncontrolled chronic pain related to cancer or its treatment
- BPI average pain >2 in previous 24 hours
- defined prior opioid and co-analgesia
- stable opioid dose for 48 hours
- stable co-analgesics 48 hours

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“Refractory pain”

- chronic pain
- previous treatment with opioids (pre-defined dose)
- previous treatment with appropriate co-analgesics
- pain ≥3/10

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Exclusion criteria

- previous ketamine for pain in last 6 months
- procedure likely to affect pain
- history of seizures
- co-morbidities that put patient at risk
- glaucoma
- psychiatric illness (excluding depression, anxiety)

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Methods

- stratified neuropathic vs nociceptive pain (LANNS score)
- 100-300-500mg/24hours sub-cut infusion ketamine/placebo
- dose escalation according to pain response
- rescue midazolam/haloperidol
- dose reduction if uncontrolled toxicity

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Methods

- continue baseline opioids (reduction allowed) in case of toxicity
- free access to breakthrough analgesia
- 5 day study intervention (or 24 hours at max dose with no improvement in pain)
- follow-up to 28 days

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Definition of a clinically relevant improvement in pain

- ≥2 point reduction in average BPI score with ≤4 breakthrough doses of opioid
- used to guide daily dose increments and primary outcome measure

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Definition of “completion”

- completed 5 days study drug
- completed 24 hours at maximum dose with no response
- stopped study drug because of intolerable side-effects

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Outcomes

- Primary outcome measure
  -pain response after 5 days intervention

- Positive response
  -a clinically relevant improvement in pain at the end of the 5 day study period

- Negative response
  -no improvement in pain at end day 5
  -no response after 24 hours at max dose
  -withdrawal with unacceptable toxicity

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Outcomes

- Secondary outcome measures
  - pain assessments days 2-5
  - adverse events
  - psychomimetic toxicity
  - Global Impression of Change
- Descriptive end points
  - QOL
  - opioid use
  - performance status
  - survival
- Economic analysis

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Hypothesis

- “Ketamine will be considered superior to placebo if there is an absolute improvement in response rate of 25% after 5 days in those randomised to ketamine compared to placebo”

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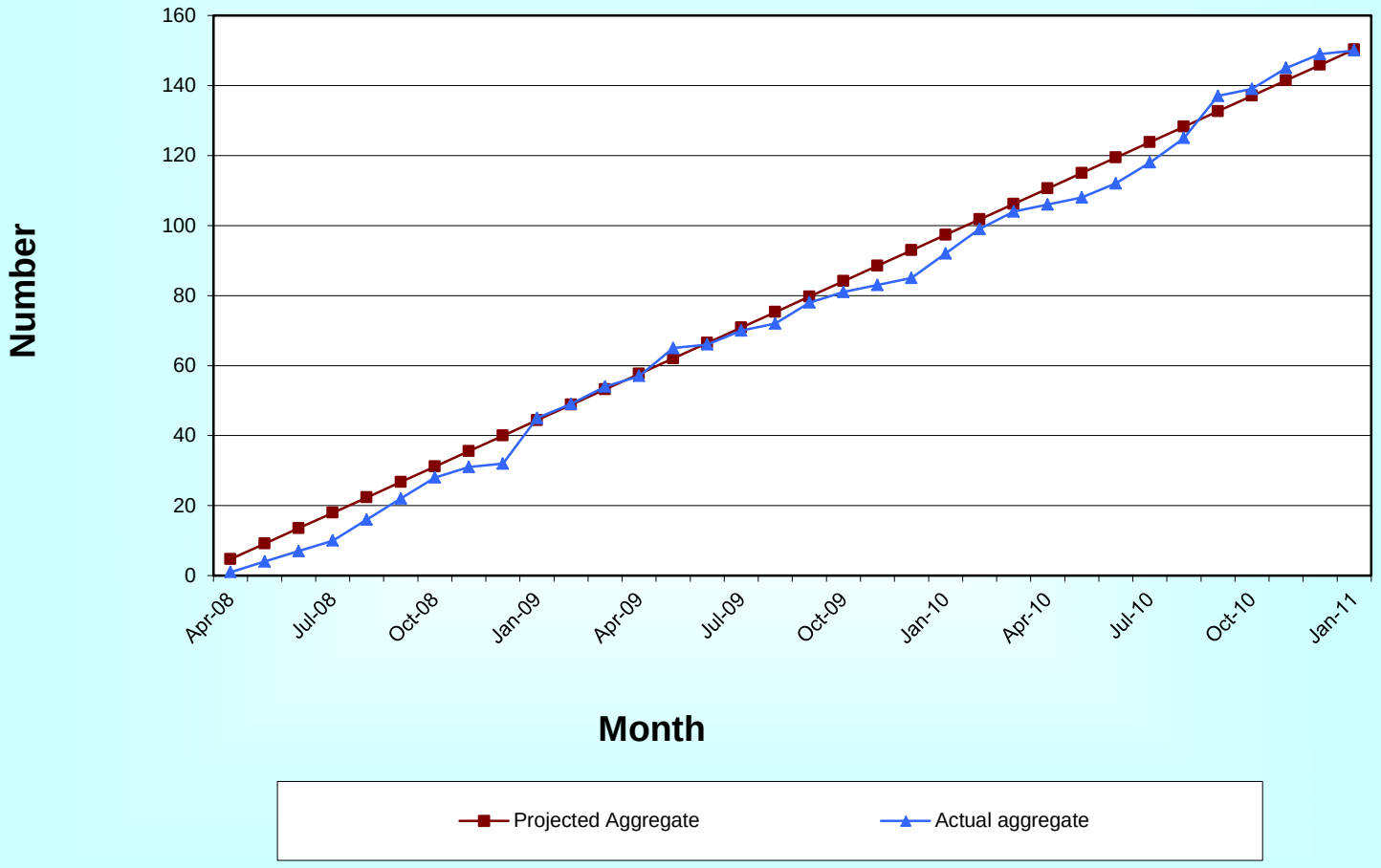
Sample size and analysis

- at least 150 completed participants, for 80% power to detect a 25% absolute difference in response rate, type 1 error 0.05

Ketamine study, completed vs expected



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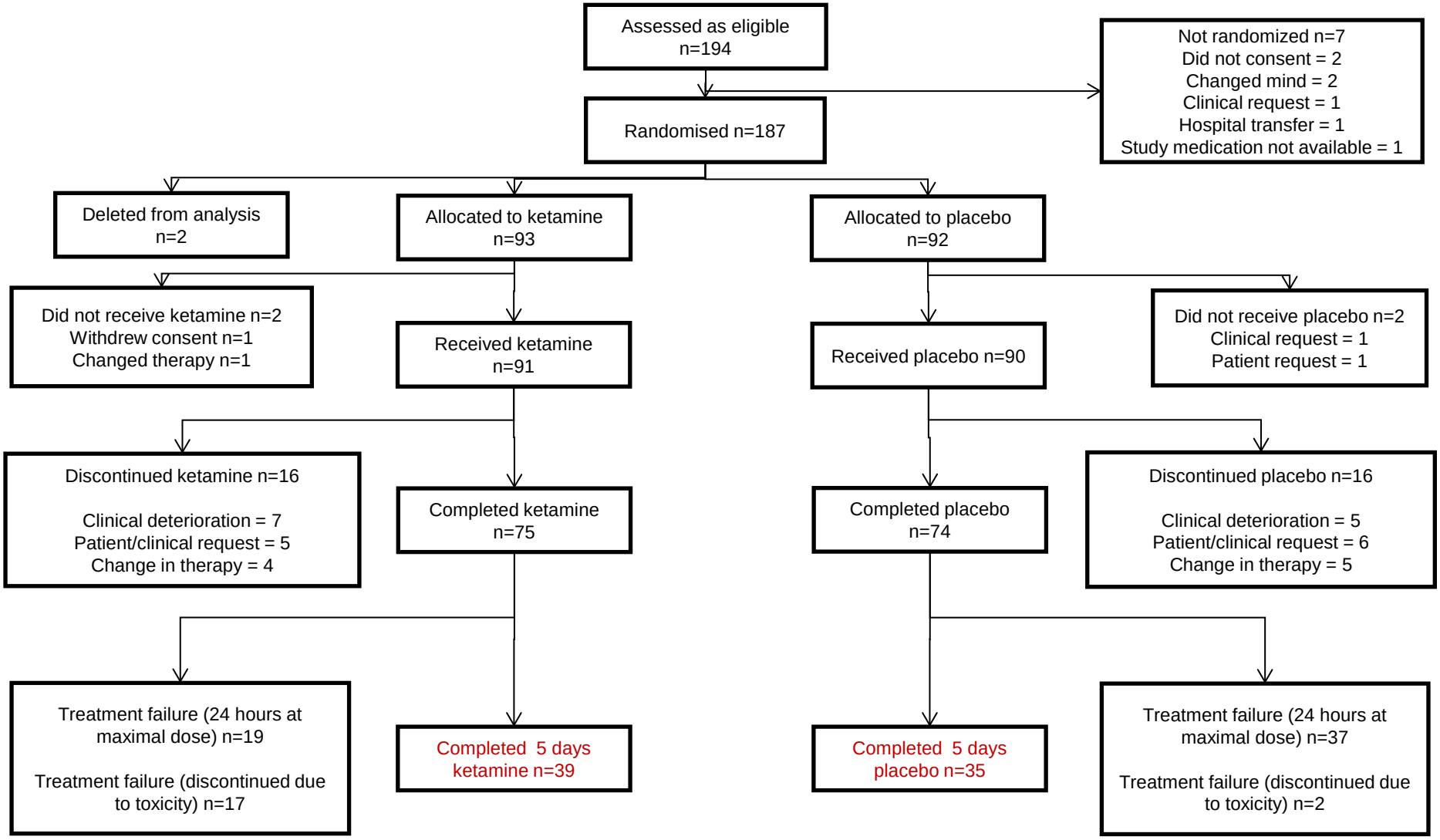
Results

- 10 recruitment sites (Qld, SA, Vic, NSW, WA)
- duration 3 years (March 08 – Feb 11)
- 187 randomised
- 2 deleted from data base
- 181 received intended treatment
  (ketamine 91, placebo 90)
- 150* completed (pain score at day 6, no response after 24 hours at max dose, unacceptable toxicity)

* 1 patient subsequently found to not meet definition

Figure 2. Participant flow



Baseline characteristics

(mean (sd), median (range) or n (%))

	Ketamine (n=93)	Placebo (n=92)
Age in years	63 (13.7)	64.3 (9.9)
Male sex	50 (55.0)	53 (58.2)
Cancer diagnosis		
Lung	22 (24.2)	18 (19.8)
Breast	6 (6.6)	11 (12.1)
CRC	8 (8.8)	14 (15.6)
Prostate	13 (14.3)	11 (12.1)
Bone/soft tissue	5 (5.6)	2 (2.2)
Gynae	8 (8.8)	3 (3.3)
Pancreas	5 (5.5)	5 (5.5)
Other	26 (28.6)	26 (28.9)
AKPS	60 (50-60)	60 (50-60)
OME	300 (160-480)	410 (258-700)

Baseline characteristics

(mean (sd), median (range) or n (%))

	Ketamine (n=93)	Placebo (n=92)
BPI pain score		
Average	5.43 (1.3)	5.21 (1.4)
Worst	8.08 (1.5)	7.64 (1.6)
Least	2.47 (1.7)	2.37 (1.9)
LANSS score ≥12	28 (30.1)	28 (30.4)
CADSS score		
0	55 (59.8)	54 (60.4)
1-2	19 (20.7)	14 (15.4)
3-8	12 (13.0)	14 (15.4)
9+	6 (6.5)	8 (8.8)
Antipsychotics	1 (1.1)	3 (3.3)
Benzodiazepines	9 (9.7)	15 (16.3)

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Adverse events at baseline

	ketamine	placebo
somnolence	39 (45.4)	32 (35.2)
constipation	37 (44.1)	42 (46.7)
N/V	26 (28.3)	21 (22.6)
dizziness	14 (16.3)	21 (23.1)
confusion	9 (9.7)	9 (9.8)
hypertension	7 (8.1)	4 (4.4)
cardiac arrhythmia	6 (6.9)	4 (4.6)
hypoxia	6 (7.1)	11 (12.4)
site irritation	5 (5.9)	5 (5.49)
other	2 92.2)	6 (6.5)

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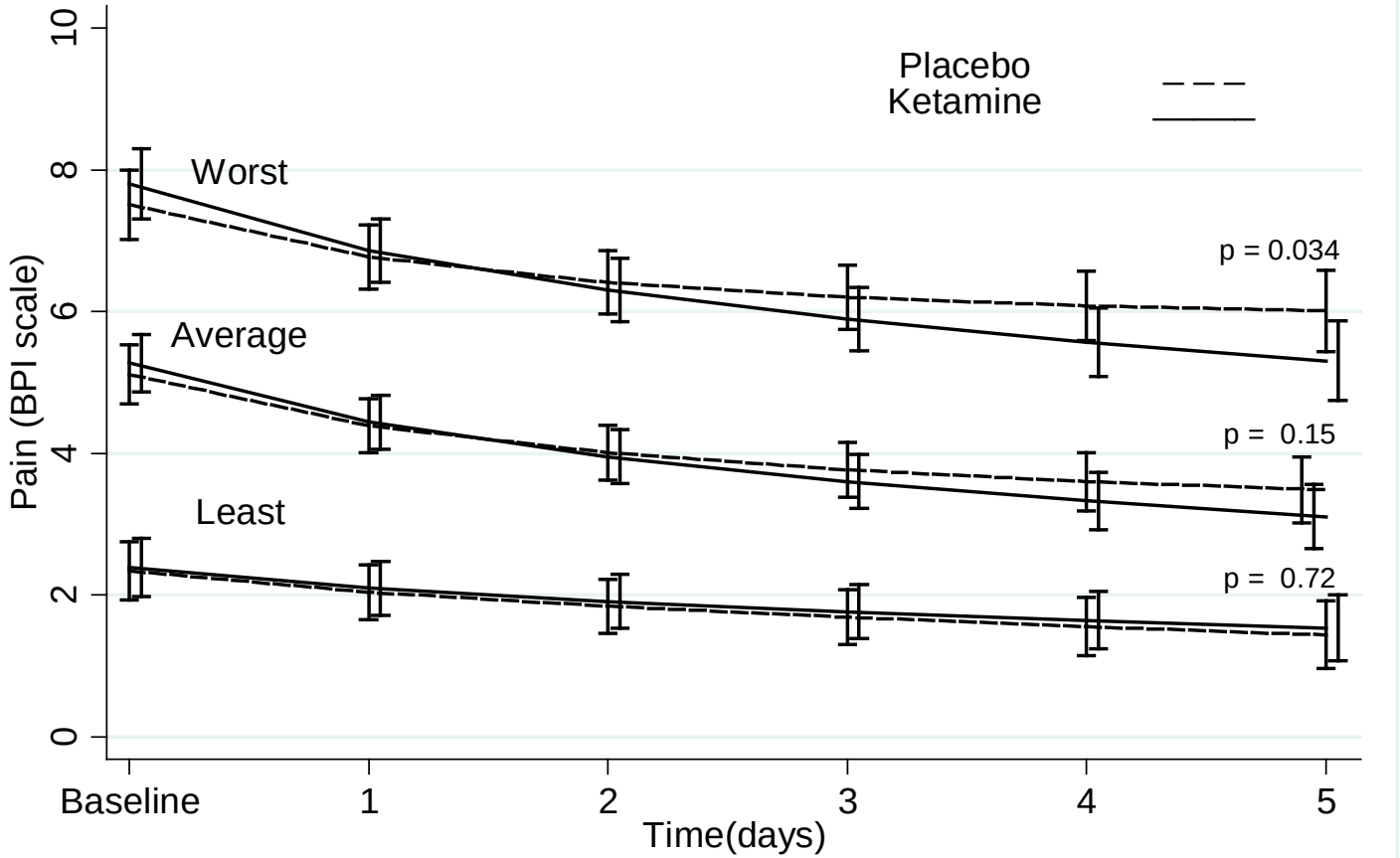
Primary analysis (Intention to treat (ITT))

- placebo response rate 25/92 = 27%
- ketamine response rate 29/93 = 31%
- no difference (p = 0.55) in proportion of positive outcomes in each group (0.04(-0.10,0.18))



p-values are differences between arms at study end
Error bars = 95% CI, n=181
Adjusted for background opioid dose, age, gender, paintype

Primary Analysis

ITT analysis p= 0.55
Ketamine 29/93 (31%)
Placebo 25/92 (27%)

Last observation carried forward (LOCF)
Ketamine 29/91 (32%)
Placebo 25/90 (28%) p = 0.55

Total completed p =0.28
Ketamine 25/75 (33%)
Placebo 19/75 (25%)

Completed 5 days p= 0.39
Ketamine 25/39 (64%)
Placebo 19/35 (54%)

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Secondary analysis

- pain type (nociceptive vs neuropathic) did not predict response or modify outcome
- no difference between arms for any given level of pain reduction, including those with marked reductions
- no difference in the number of breakthrough doses given in each arm

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Unit response

Score change	Placebo (n=90)	Ketamine (n = 91)
1	50 (56%)	59 (65%)
2	34 (38%)	39 (43%)
3	19 (21%)	24 (26%)
4	8 (9%)	13 (14%)
5	3 (3%)	6 (6%)
6	1	3

Number of adverse events occurring in which the grade was worse than baseline.

	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

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Adverse events

- Participants on ketamine:
- had almost twice the incidence of AEs worse than baseline

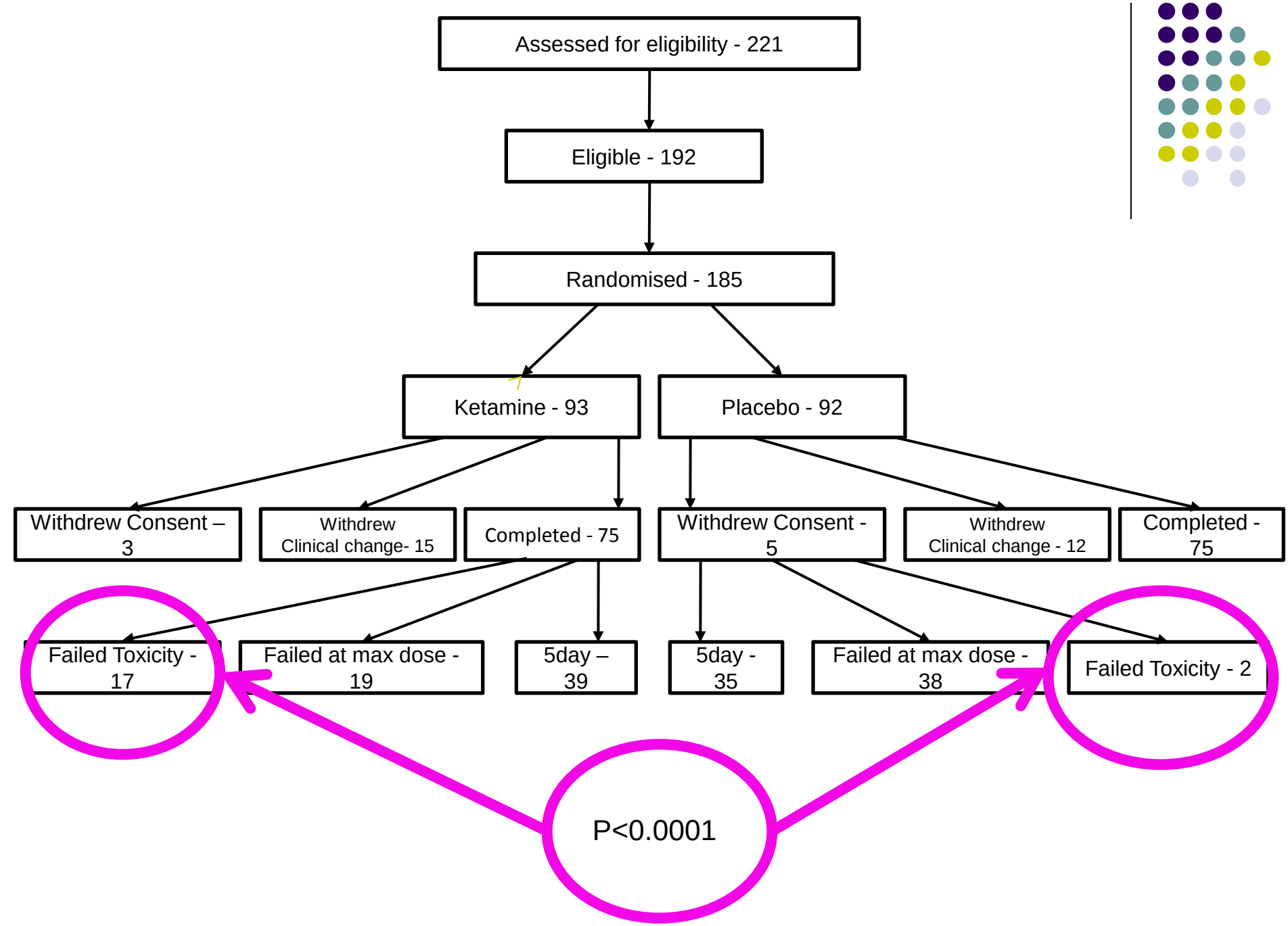
  e.g. for day 1 IRR = 1.95 (1.46, 2.61) p<0.001
- were more likely to experience a more severe grade of AE/day

  OR=1.09 (1.00, 1.18), p=0.039
- were 3x more likely each day to report an injection site reaction

  OR= 2.85 (1.77, 4.73) p<0.001.

- few AEs >grade 3 (ketamine 14, placebo 16)

  light-headedness, somnolence, hypoxia
- 7 SAEs : 2 thought possibly related to study drug (bradyarrythmia, cardiac arrest)


Assessed for eligibility - 221
Eligible - 192
Randomised - 185
Ketamine - 93
Placebo - 92
Withdrew Consent – 3
Withdrew Clinical change- 15
Completed - 75
Withdrew Consent - 5
Withdrew Clinical change - 12
Completed - 75
Failed Toxicity - 17
Failed at max dose - 19
5day – 39
5day - 35
Failed at max dose - 38
Failed Toxicity - 2
P<0.0001

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Psychomimetic toxicity

- 40% of all participants had a positive score at baseline, no diff between arms
- odds of ketamine participants experiencing psycho-toxicity increased each day, significant after day 3

  (OR 2.53;1.11-5.78;p=.027)
- Ketamine group more likely to report higher scores each day (p=.093),
- significant difference by study end

  (ß = 0.46;0.4-0.88;p=.034)

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Results

- NNT = 25 (6,∞)

-number needed to treat for one additional patient to get a positive outcome

- NNH = 6 (4,13)

- withdrawal because of toxicity

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Conclusion

- this study confirmed the very high placebo response rate predicted
- subcutaneous ketamine had no benefit over placebo in the management of chronic pain related to cancer or its treatment for 5 days when used in a dose escalating regimen
- significantly more toxicity in the ketamine group

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RCT evidence

1. Oral racemic ketamine, S-ketamine and placebo

-*discontinued at interim analysis as no difference btwn groups*

2. Dose escalating subcut ketamine vs N/saline over 5 days

- *no difference between arms, more toxicity with ketamine*

3. Oral racemic ketamine vs placebo in neuropathic pain

Wilcock et al :JPSM, Therapeutic review August 2015

Recommendations:

By mouth: 10mg prn – 200mg qid

Subcut: 2.5mg prn – 500mg/24hours

IV: 2.5mg prn – 1mg/kg or 60mg over 4 hours

References: personal communication - RCT

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- Janet Hardy, Steve Quinn, Tania Shelby-James, Belinda Fazekas, Meera Agar, Odette Spruyt, Peter Allcroft, Phillip Good, Katherine Clarke, Christine Sanderson, Jenny Phillips, Simon Eckermann, Nikki McCaffrey, John Plummer, Debra Rowett, Derek Eng, Richard Chye, Patsy Yates, David Currow

- Michael Ashby, Kristen Auret, Paul Glare, Liz Whyte, Lyn Oldham, Kate Jackson, Amy Abernethy


#PAIN#