Ketamine

Ruth Clark and Kath Mitchell

Aims and Objectives

- To give an overview of mechanism of action of ketamine
- To give a brief Literature Review
- To review dosing, routes of administration, side effects, contraindications and monitoring
- To review supply issues and recent CD regulations
- To review successful and unsuccessful case studies of ketamine usage
- To present 'Merseyside and Cheshire Palliative Care Network Audit Group' audit

NMDA Receptor

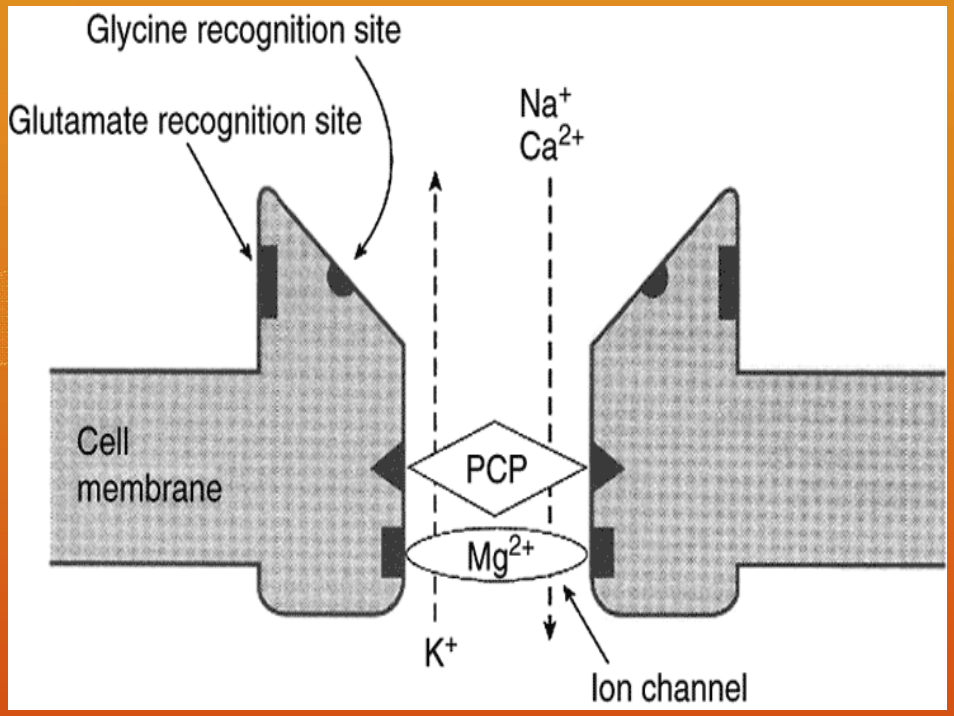


Figure 1 Diagram of the NMDA (excitatory) receptor-channel complex. The channel is blocked by Mg^{2+} when the membrane potential is at its resting level (*voltage-dependent block*) and by drugs which act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g. dextromethorphan, ketamine, methadone (*use-dependent block*).[4]
* reproduced with permission from palliativedrugs.com

- Involved with sensitisation of the dorsal horn neurones which transmit pain signals
- At rest the channel is blocked by magnesium
- Prolonged stimulation or excitation unblocks the channel and calcium moves into the cell
- Leading to neuronal hyper-excitability
  - Hyperalgesia
  - Allodynia
  - Reduction in opioid responsiveness

Ketamine

- Anaesthetic agent
  - with a role in treatment of pain unresponsive to standard treatments at sub-therapeutic doses
- A potent NMDA receptor channel blocker
  - Binds to channel sites when open and activated
  - Antagonises the hyper-excitation state

Ketamine

- In addition ketamine has multiple receptor interactions
  - Interacts with other calcium and sodium channels
  - Dopamine receptors
  - Cholinergic transmission
  - Noradrenergic and serotoninergic re-uptake
- Opioid like and anti-inflammatory effects

Ketamine

- In the UK, licensed product is a racemic mixture
- *S*-enantiomer and *R*-enantiomer
- Individual enantiomers are more potent than the mixture
- Bioavailability - parenterally 93%, orally 17% (extensive 1st Pass metabolism)
- Oral Ketamine → Norketamine (equipotent in terms of analgesia)
- Long term use leads to hepatic enzyme induction and enhanced ketamine metabolism

The Literature Review

Cochrane Collaboration 2012

- *Bell, Eccleston and Kalso 2012*
- To determine the effectiveness and adverse effects of ketamine as an adjuvant to opioids in the treatment of cancer pain
- **Selection criteria** adult, cancer, on opioid, received ketamine or placebo/active control

Cochrane Collaboration 2012

- **Data** 7 RCTs (5 excluded, poor design) and 32 case studies/case series reports
- **Results** 2 trials included, small numbers of patients, results could not be pooled
- **Conclusion** More RCTS needed, current evidence insufficient to assess benefits and harm

	Mercandante 2000	Yang 1996
No of patients	10	20
Sex	7 male, 3 female	10 male, 10 female
Age range	21-69yrs	22-69yrs
Pain	Pain unrelieved with morphine. Pain classed as "neuropathic" or having a "neuropathic component"	Cancer pain effectively treated with morphine
Intervention	2 doses ketamine IV bolus 0.25mg/kg and 0.5mg/kg as adjuvant to morphine vs. saline 2 day washout between treatments No rescue doses described	Intrathecal 1mg/kg ketamine as adjuvant vs. morphine alone Morphine dose titrated until stable for 48 hrs then randomly crossed over to morphine + ketamine or continued on morphine (control) alone, administered twice daily intrathecally No washout period Rescue doses available of morphine 5mg IM
Outcome measures	Patient-reported pain intensity at 30, 60, 90, 120, 180 minute intervals and adverse effects Pain score 0-10 numerical scale	Patient-reported pain 0-10 numerical scale Pain frequency Group morphine dose Total titrated intrathecal morphine Total rescue doses Frequency of intrathecal titration
Effectiveness	<u>0.25mg/kg dose</u> Pain score reduced after 30 mins vs. saline After 60 mins effect lessened but some benefit even after 180 mins noted <u>0.5mg/kg dose</u> Significant reduction at 30 mins and maintained throughout the 180 mins	Co-administration of ketamine reduced the dose of morphine needed Was as effective as intrathecal morphine alone

Adverse effects

- No withdrawals in either study documented
- 4 patients experienced hallucinations with IV ketamine (3 at both doses and 1 extra at higher dose). Treated with diazepam 1mg.
- Two of the four patients also experienced light flashes, a “buzzing” feeling in the head and a sensation of insobriety. Diazepam resolved these symptoms.
- Increased drowsiness was reported with IV ketamine
- Other adverse effect reported from intrathecal group included: pruritis, constipation, urinary retention, difficulty in urinating, nausea and vomiting, hallucinations, respiratory depression.
- Cannot be attributed to study medication as some present beforehand. Hallucinations reported in morphine only arm.

Conclusions

- No evidence based conclusion due to small numbers
- There are a number of randomised studies that could provide further evidence in the future that have not been published yet, being finalised or still recruiting!

Other Reports

- 32 case reports or open label uncontrolled trials
- To treat refractory cancer pain, frequently described as neuropathic pain
- Mostly opioid AND ketamine
- Total of 246 patients
- Various routes used po ,im ,s/c bolus and infusion ,iv bolus and infusion , epidural bolus, intrathecal infusion
- Various doses 1mg/kg/day s/c infusion to 600mg/day iv, 67.2mg/day intrathecal
- Various time scales from 4 hours to 12 months

Case Studies

- Most used morphine, some fentanyl, hydromorphone, diamorphine
- Ketamine used as sole analgesic in 3 reports
- 16 reports described dramatic relief of refractory cancer pain
- Commonest adverse effects sedation and hallucinations
- One had sedation settling with opioid reduction
- Only 2 studies out of 32 had patient withdrawal
- Other side effects – inflamed infusion sites, nystagmus, hyperalgesia post cessation

NICE: Chronic Pain, Oral Ketamine

- 2 small, short term, randomised, placebo-controlled trials and 1 small case series of n-of-1 trials provide no good quality evidence for the use of oral ketamine

Therefore…

- Evidence of efficacy is mainly from case reports, retrospective surveys and uncontrolled studies

Oral Ketamine

- 10-25mg TDS/QDS and PRN
- Titrate up in steps of 10-25mg up to 100mg QDS
- Maximum reported dose 200mg qds
- Consider dose reduction if drowsy/psycho-mimetic issues
- Can have opioid sparing effect
- Unlicensed preparations, various strengths and flavours

“Burst” Ketamine

- Start with 100mg/24 hrs.
- If not effective increase to 300mg/24 hrs.
- If not effective again, increase to 500 mg/24 hrs.
- Stop 3 days after last dose increment
- Use maximal dilution and 0.9% sodium chloride
- Prophylactic use of e.g. diazepam, midazolam or haloperidol recommended

1. Therapeutic reviews - Rachel Quibell, Eric Prommer, Mary Mihalyo, Andrew Wilcock and Robert Twycross
Journal of Pain and Symptom Management Volume 41, March 2011

Other routes

- Intravenous
- Continuous subcutaneous infusion
- Mouthwash
- Sublingual

Cautions

- Acute porphyria
- Any situation where a rise in blood pressure or intracranial pressure would be hazardous
- History of psychiatric disorders
- Epilepsy
- Cardiac conditions – heart failure, ischaemic heart disease, CVAs
- Hyperthyroidism

Interactions

- Plasma concentration raised by diazepam, CYP3A4 inhibitors e.g. clarithromycin, ketoconazole

Undesirable effects

- Dose related
- Psychomimetic – euphoria, dysphasia, blunted affect, vivid dreams and nightmares, inattention, memory, illusions, hallucinations, altered body image
- Delirium, dizziness, diplopia, blurred vision, nystagmus, hearing, HYPERTENSION, tachycardia, hyper salivation, nausea and vomiting, injection site erythema, URINARY TRACT TOXICITY

Urinary Tract Toxicity

- Unclear of cause, direct irritation or metabolites
- Frequency, urgency, urge incontinence, dysuria, haematuria
- Interstitial cystitis, detrusor over activity, reduced bladder capacity, vesico-ureteric reflux, hydronephrosis, papillary necrosis, renal impairment

- If symptoms of urinary tract infection and NO evidence of bacterial infection, consider discontinuing and seeking Urology review
- Symptoms settle in a few weeks, gradual reduction in dose ideally to prevent pain escalation

- Therapeutic Reviews[1] – Advise long term ketamine only if "Burst" has failed in patients with a prognosis of months to years

1. Therapeutic reviews - Rachel Quibell, Eric Prommer, Mary Mihalyo, Andrew Wilcock and Robert Twycross
Journal of Pain and Symptom Management Volume 41, March 2011

Monitoring

- Can have an opiate sparing effect – some clinicians reduce opiate dose by 25-50% especially when starting subcutaneous ketamine
- If drowsy, consider an opiate reduction
- Merseyside and Cheshire Palliative Care Network Audit Group Guidelines
  - LFTs prior to treatment and at regular intervals if long term
  - Blood pressure and pulse rate prior to treatment and twice daily during titration phase or whole duration of 'burst' ketamine
  - Respiratory rate twice daily during titration phase or whole duration of 'burst' ketamine
  - Pain score prior to treatment and throughout to monitor effectiveness and need for dose titration

Marie Curie Cancer Care

MARIE CURIE CENTRE
LIVERPOOL
KETAMINE OBSERVATION CHART

Patients Name ..... **D.O.B.** ..... **Team** .....

Date Commenced Ketamine ..... **Oral or S/C** ..... **Infusion or Bolus Doses:** .....

Baseline Observations:

Date	Dose	Time	BP	Pulse	Pain Score	Pupil Size	Resps	Conscious Level	Cognitive Function	Comments: Also see Careplan

L:\Forms\General office & administration\WARDSMASTER\JULY2012\Ketamine Observation Chart.DOC

NURSING CHECKS

Pain Score Score 0 = No pain at all
Up To Score 10 = Worst pain imaginable

Pupil Size
- N = Normal
- D = Dilated
- P = Pinpoint

Conscious Level
- Score O = Normal (patient awake and alert)
- Score S = Sleep (normal sleep, easy to wake)
- Score 1 = Drowsy (easy to wake)
- Score 2 = Very drowsy (difficult to wake)
- Score 3 = Unconscious

Cognitive Function
- N = Normal
- C = Some episodes of confusion
- A = Some episodes of agitation
- V = Vivid dreams
- H = Hallucinations
- D = Feelings of disorientation

RATIONALE

To monitor the patients level of pain and the effectiveness of Ketamine as an analgesic

To observe for opioid toxicity

Conscious level and resps. checked to observe for opioid toxicity

To observe for opioid toxicity and also potential side effects of Ketamine in certain situations e.g. overdose or individual patient incompatability

- Other observations checked to observe for opioid toxicity and side effects of Ketamine in its use in palliative care as an analgesic.

Other Information

- Withdrawal of ketamine over 2-3 weeks if long term
- Benefits of a short course can last weeks or even months
- Burst ketamine can be repeated as required
- Don’t stop abruptly if treatment greater than 3 weeks – risk of hyperalgesia and allodynia

- Conversions
  - Evidence is limited
  - From PO to SC for CSCI, suggested 1:1 conversion
  - From SC to PO, suggested 3:1 conversion
  - Due to norketamine, blood concentrations greater after oral administration

Ketamine-the legal bits

- 2005-2014 class C. 2014- class B
- MDA 1971 controls dangerous/harmful drugs. A framework for criminal penalties wrt harm or possible harm when drug misused or illegal activity undertaken in regard to that drug. Harm assessed by ACMD.

The legal bits

- Misuse of drugs regulations 2001 regulates availability of CDs via schedules recognising use in medicine/research
- Schedule dictates extent of control

- Ketamine is schedule 1V part 1

But ACMD (dec 13) advising moving to sch 11

Supply

Issues-

- When using by burst need to be able to access the injectable preps. Various strengths available but currently supply problems
- Using the oral-unlicensed specials products some are fridge lines. Different flavours available. Fridge lines if sch 11.

Red drug in some areas or amber-who supplies/monitors?

- Costs injectable- 50mg/ml 2ml amps £38/10

Oral preps-50mg in 5ml 100ml £19.22 to £188.44

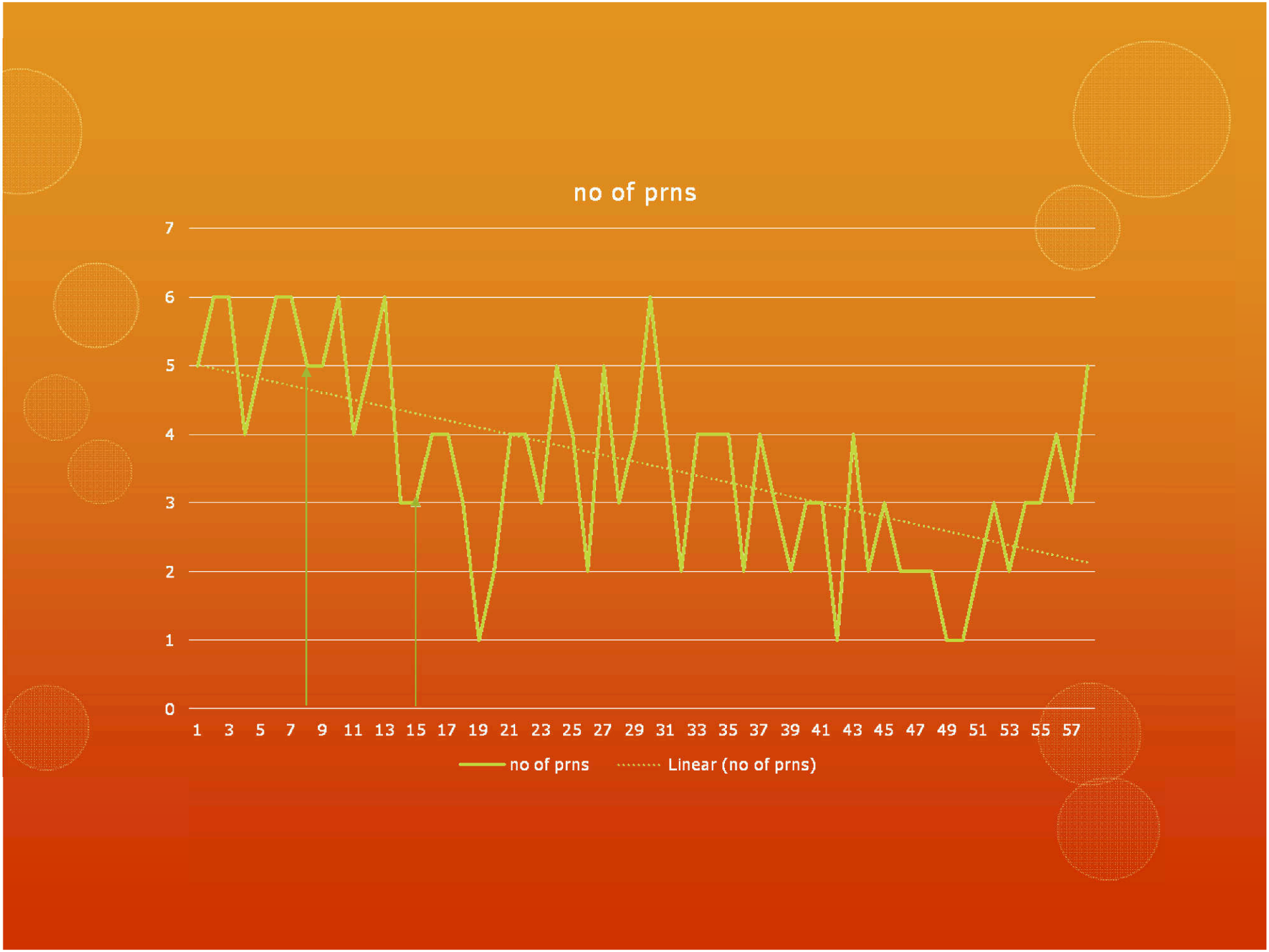
or larger bottles 500mg for £200.44

- What to do at EoL-community usually supplied through the company to a nominated pharmacy
- Conversion from oral-sc

Burst ketamine “success”

- 67 year old lady adm from hospital-Ca rectum
- Aim of admission-less pain
- Admission meds

Paracetamol 1g qds / duloxetine 60mg daily / pregabalin 150mg bd / alfentanil 8mg csci / oxycodone ir oral 15-20mgprn (5-6 doses per day) / docusate 200bd prn / Movicol 1 bd / omeprazole 20mg daily


no of prns
7
6
5
4
3
2
1
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57
no of prns
Linear (no of prns)

Burst ketamine “failure”

- 50 year old man diagnosis oesophageal cancer
- Previous problem with mood. Psychiatric input.
- Mid april drowsy myoclonic unwell sent to A& E. “pain better controlled” switched morphine to oxycodone but then 1 week later- Struggling with pain at home
- Admitted 1.5.14 for burst ketamine

Drugs on admission-

- Oxycontin 100 bd+30mg prn oral/paracetamol 1g qds

/pregabalin 300mg bd/amitriptyline 75mg night/venlafaxine 225mg night/omeprazole 40mg daily/metoclopramide10mg tds/codanthrusate 2 bd/Laxido 1 sachet od

So what did we do?

- 1.5.14 – prescribed ketamine 100mg sc for 24 hrs & haloperidol 1.5mg night. Decreased Oxycontin by 30% to 70mg bd.
- 2.5 - reported poor night. Ketamine 300mg prescribed, started naproxen 500mg bd and physio issued tens machine. Tolerating ketamine ok
- 3.5.14 Ketamine increased to 500mg but was still in significant pain overnight
- 4.5.14 pain issues overnight but better in the morning dose held at 500mg
- 5.5.14 still on 500mg sc doesn't feel there has been any benefit from ketamine or naproxen

What happened next

- 6.5.14 to stop ketamine/haloperidol/naproxen. Keep oxycodone mr same added dexamethasone 8mg bd trial for 3/7. Start clonazepam 500 micrograms night
- Consider methadone
- 7.5 early signs dex having an effect
- 8.5 methadone started modified Morley Makin regime
- 10.5 feels methadone has made a big impact on his pain
- (so much so he went home & drove his car!)

An oral ketamine success?

- Joe-60+year old with Ca prostate diagnosed oct 2010

with metestatic spread to ribs & back-spinal decompression + XRT jan 11. Admission 15th aug 11 for pain control.

DH-

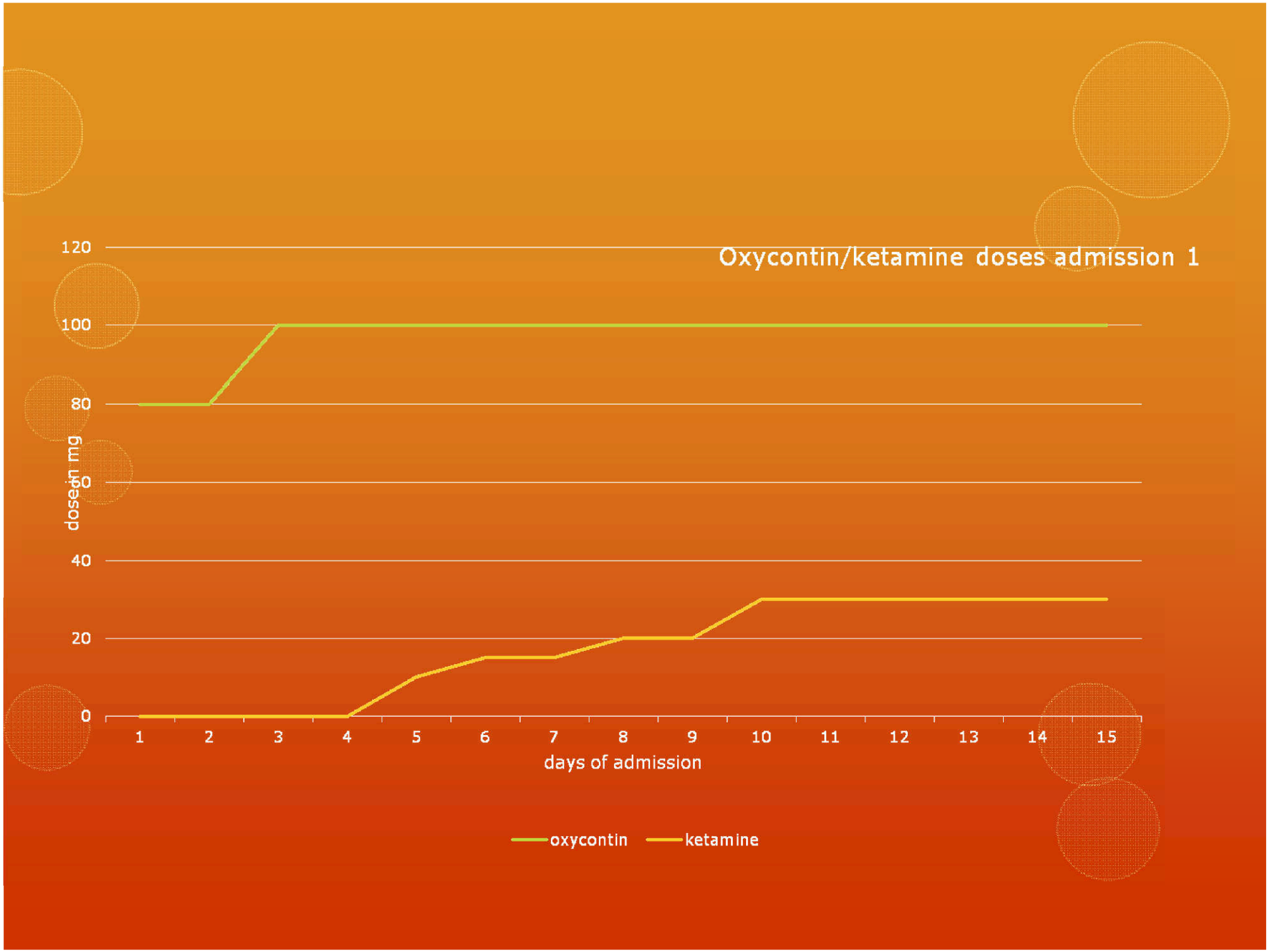
Pain-

Other problems-

Initial plan-

Progress

- 15.8 opioid switch Oxycontin 80 bd
- 17.8 Oxycontin inc 100bd gabapentin to pregabalin switch
- 19.8 ketamine 10-20 qds + haloperidol 1.5mg
- 20.8 15mg
- 22.8 20mg
- 24.8 30mg
- 25.8 pain score change 6-8 to 2 disch 30.8
- Re admit 22.11.11 –waiting for spinal surgery “loose screws/metal work”


Oxycontin/ketamine doses admission 1
120
100
80
60
40
20
0
dosein mg
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
days of admission
oxycontin
ketamine

Re-admission 22.11.11

- 20.11.11 ketamine inc to 40mg qds
- 21.11.11 inc to 50mg qds
- 22.11.11 admitted
- 23.11 “jerky” Oxycontin dec to 80 bd
- 30.11 Disch home then surgery 12.12.11

Ongoing-

- Discharged from hospital ketamine 50mg qds/pregabalin 150mg bd/Oxycontin 80mg bd (no diclofenac)
- 17.12.11 post op discomfort but back pain improved Oxycontin to 75mg bd
- 18.7.12 restarted diclofenac for knee pain
- 15.8 Oxycontin 70mg bd/diclofenac 50 tds/pregabalin 150mg d/ketamine 50mg qds -weight inc 3 stone
- 29.8 ketamine dec to 40mg qds
- 11.9 back to 50mg
- 1.13 inc back pain pregab inc to 200bd
- 2.13 Pain team-lose weight/TENS/exercise
- 4.13 monthly zoledronic acid (urology)

To end his tale-

- 6.13 Oxycontin inc to 80mg bd
- 7-9.13 amitriptyline 25-35mg (sleep)
- 9.13 zoledronic acid “no effect on pain”
- 11.13 pain ok
- 12.13-1.14 dec ketamine 40mg qds but back to 50
- 3.14 using prns amitriptyline to 50 mg
- 4.14 pregabalin inc to 250 bd for back pain but drowsy so amitriptyline dec
- 8.14 drowsy so dec pregabalin back to 200mg
- Nov 14 still with us & we supply ketamine monthly

Merseyside and Cheshire Palliative Care Network Audit Group

- Produce standards and guidelines for a variety of conditions, treatments
- In excess of 45 Guidelines
- Extensive literature review performed
- Audits performed to gain knowledge of practice
  - Retrospective/prospective case audits
  - Healthcare professionals practice audits
- Standards and Guidelines re-audited and reviewed
- In process of reviewing all audits to gain NICE accreditation
- www.mccn.nhs.uk

Use of Ketamine as an Analgesic in Palliative Care

Dr Anthony Thompson[1], Dr Graham Whyte[2], Dr Helen Bonwick[3], Ruth Clark[3], Dr Sarah Fradsham[3], *Dr Aileen Scott*[1], Dr Alison Coackley[1,4], Agnes Noble[4], Andrew Dickman[5]

1.Willowbrook Hospice, Prescot 2.Aintree University Hospitals NHS Foundation Trust 3.Marie Curie Hospice, Liverpool 4.The Clatterbridge Cancer Centre NHS Foundation Trust 5.Marie Curie Palliative Care Institute Liverpool

INTRODUCTION

Ketamine is a general anaesthetic agent which is also used as an analgesic in palliative care. Its actions include antagonisation of the NMDA receptors which leads to the analgesic effect at sub anaesthetic doses. It has several routes of administration, most commonly orally and subcutaneously. Several regimens have been described in the literature but the evidence base is lacking.

AIMS

Within the framework of a regional audit programme, we aimed to:

- Explore attitudes and current practice of specialist palliative healthcare professionals (HCPs) towards the use of ketamine as an analgesic.
- Produce regional guidelines to help assist HCPs in their practice, with the ultimate aim of providing higher quality of patient care.

DESIGN & METHODOLOGY

Following a comprehensive literature review, two data collection tools were developed and distributed. The first was a survey of HCPs to evaluate their current practice in using ketamine. This included questions on preferred route of administration, titration regimens and concomitant prescribing. The second survey focused on use of ketamine in individual patients over the seven month data collection period.

RESULTS

50 professionals responded to the survey, of whom 58% had been involved in the initiation of ketamine in the previous 12 months. Professionals' confidence in using ketamine varied. Respondents were also given the opportunity to answer similar questions about the use of methadone as an analgesic, and confidence was higher using ketamine compared to methadone.

Professional group	Confidence using ketamine	Confidence using methadone
Consultant	8.4/10	6.8/10
StR	5.6/10	4.8/10
SSAS	5.4/10	5.6/10
CNS	1.6/10	1.6/10

Figure 1 Confidence in using ketamine and methadone by professional group

A total of 39 uses of ketamine were reported during the seven month data collection period. Professionals expressed equal preference for oral and subcutaneous routes. However, in practice the subcutaneous route was more commonly used.

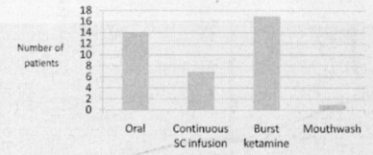


Figure 2 Routes used to administer ketamine

The level of monitoring performed on patients using ketamine varied between units. There was variation in pre-use checks and monitoring following initiation.

Test	Checked pre-use	Checked post-use
Heart rate	24	28
Blood pressure	23	28
U&E	34	25
LFT	32	23

Figure 3 Patient checks prior to and following use of ketamine N=39

Figure 4 illustrates the dose of opioid each patient was taking when they commenced ketamine, as the equivalent total daily dose of oral morphine. The average dose of opioid was the equivalent of 250mg of oral morphine in 24 hours .

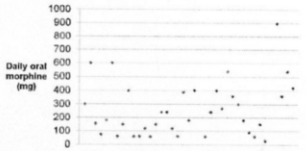


Figure 4 Equivalent total daily dose of oral morphine of each patient switched to ketamine

Most patients were also on adjuvant analgesics, most commonly the neuropathic agents Pregabalin and Gabapentin.

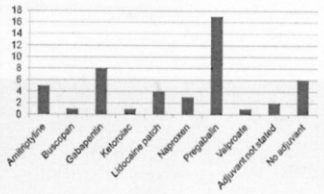


Figure 5 Number of patients using each adjuvant at the time of commencing ketamine

Ketamine is known to have an opioid-sparing effect, which may lead to opioid toxicity in some patients. However most patients did not require their opioid dose to be altered following the initiation of ketamine. Another potential side effect of ketamine is urinary tract toxicity, however no patient in the audit experienced this.

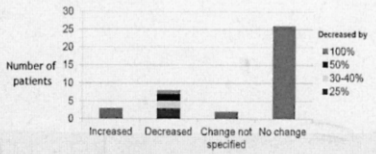


Figure 6 Change in opioid dose following commencement of ketamine

CONCLUSIONS

Ketamine is increasingly being used as a co analgesic in palliative care. Despite this there is variation in regimens and doses. The literature suggests that burst ketamine should be considered in the first instance due concerns regarding long term side effects of ketamine including urinary toxicity.

Following this audit regional guidelines have been produced to assist healthcare professionals in their practice in the use of ketamine. Further evidence is needed to increase the evidence base and support the regimens used in clinical practice. All units administering ketamine should have a comprehensive policy.

REFERENCES

Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database of Systematic Reviews 2012* DOI: 10.1002/14651858.CD003351.pub2

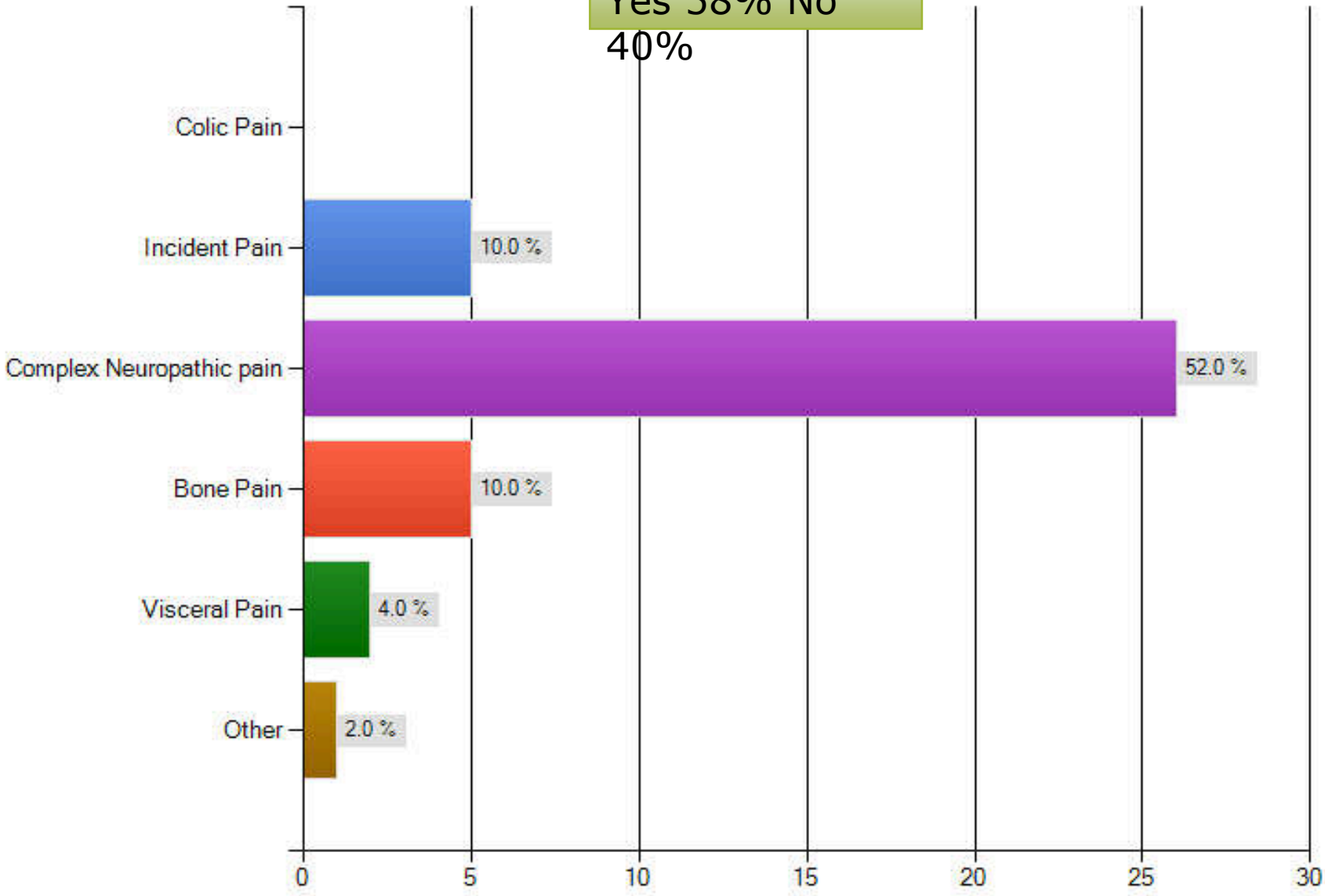
Fallon MT, Welsh J. The role of ketamine in pain control. *European Journal of Palliative Care* 1996:3:143-6

Quibell R, Prommer E, Mihalyo M, Twycross R, Wilcock A. Therapeutic review: Ketamine. *Journal of Pain and Symptom Management* 201142:640-9

Healthcare Professionals Audit results (n=50)

Have you been involved in starting ketamine in a palliative care patient in the last 12 months? If yes, in which of the following types of pain scenarios would you consider using ketamine?

Yes 58% No 40%



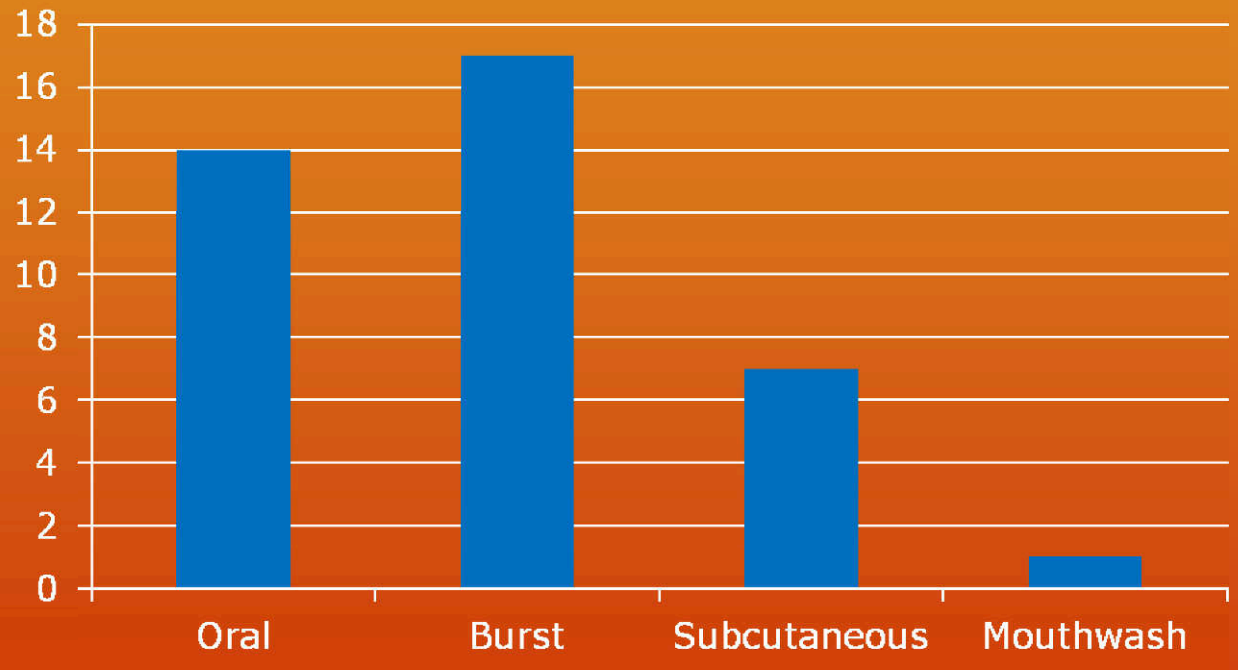
Professional Group	Started Ketamine in last 12months	Confidence using ketamine
Consultant	85%	8.4/10
StR	78%	5.6/10
SSAS	80%	5.4/10
CNS	21%	1.6/10

What route of administration do you use?

- Equal preference for Burst and Oral Ketamine
- Burst 100mg/24 hours up to 500mg/24 hrs 5-7 days
- Oral 10 mg tds – most common dosage.

Prospective data collection of current practice (n=39)

Route used

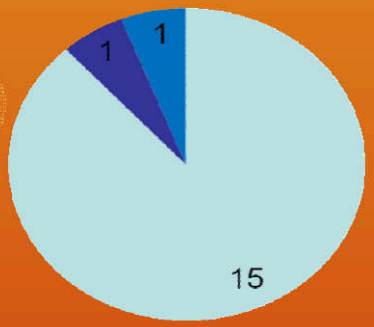


Oral:
Starting dose range 5-20mg TDS
Maximum dose range 15-100mg TDS

Additional medication

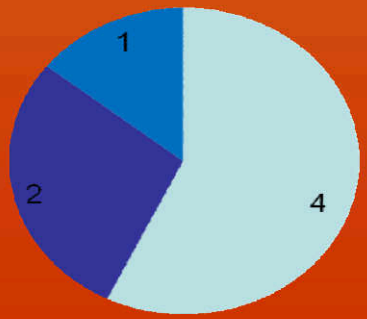
Haloperidol
Benzodiazepine
None

Oral



Haloperidol
Midazolam
Haloperidol and Midazolam

Burst Ketamine

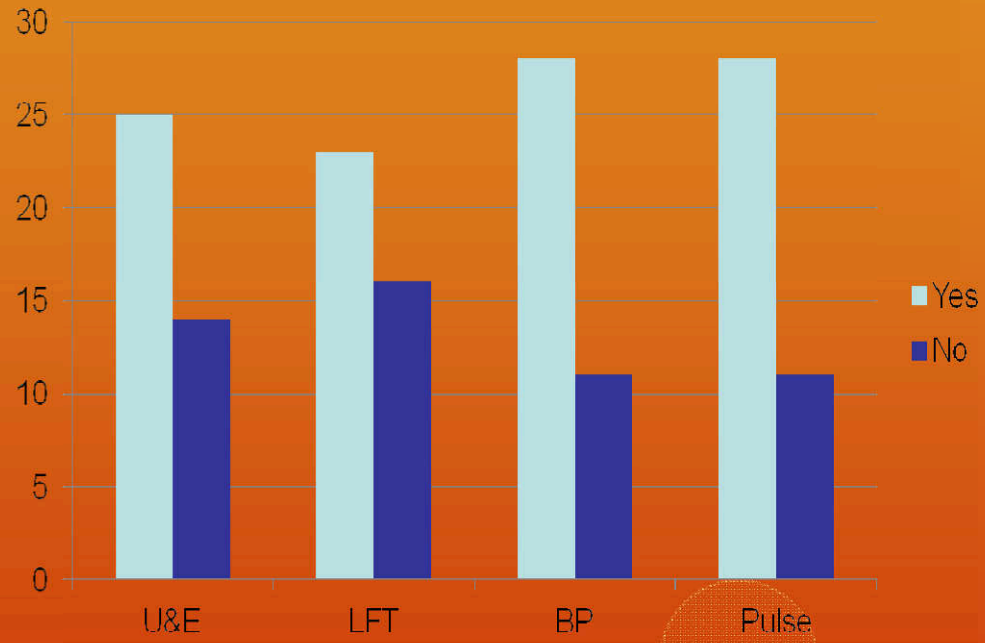


Midazolam
Haloperidol
None

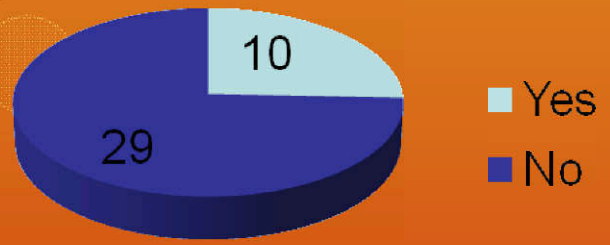
Continuous subcutaneous infusion

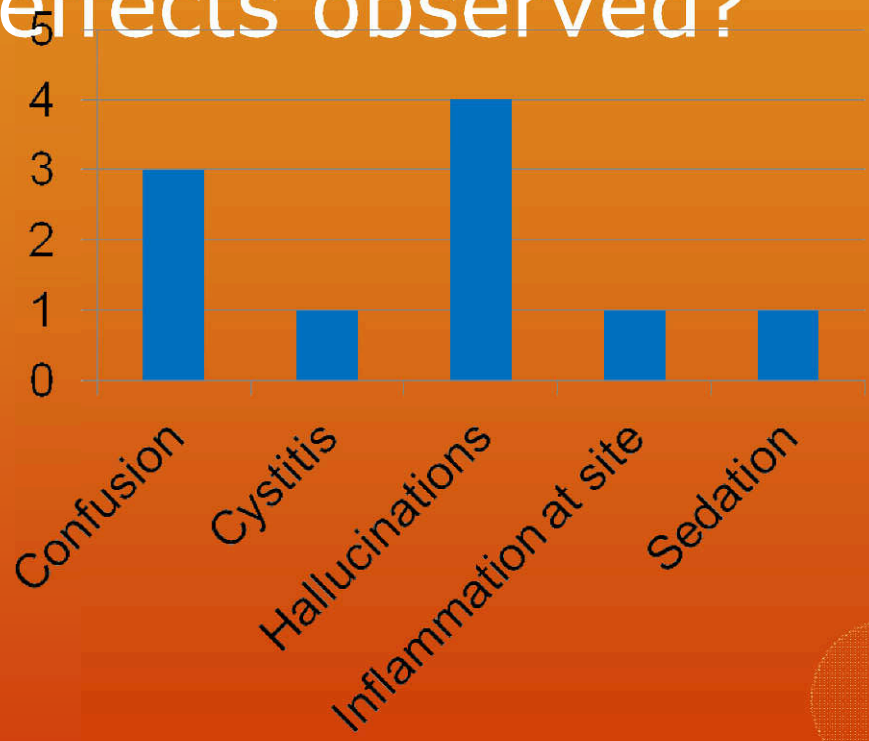
Pre-use checks

Checks after ketamine commenced

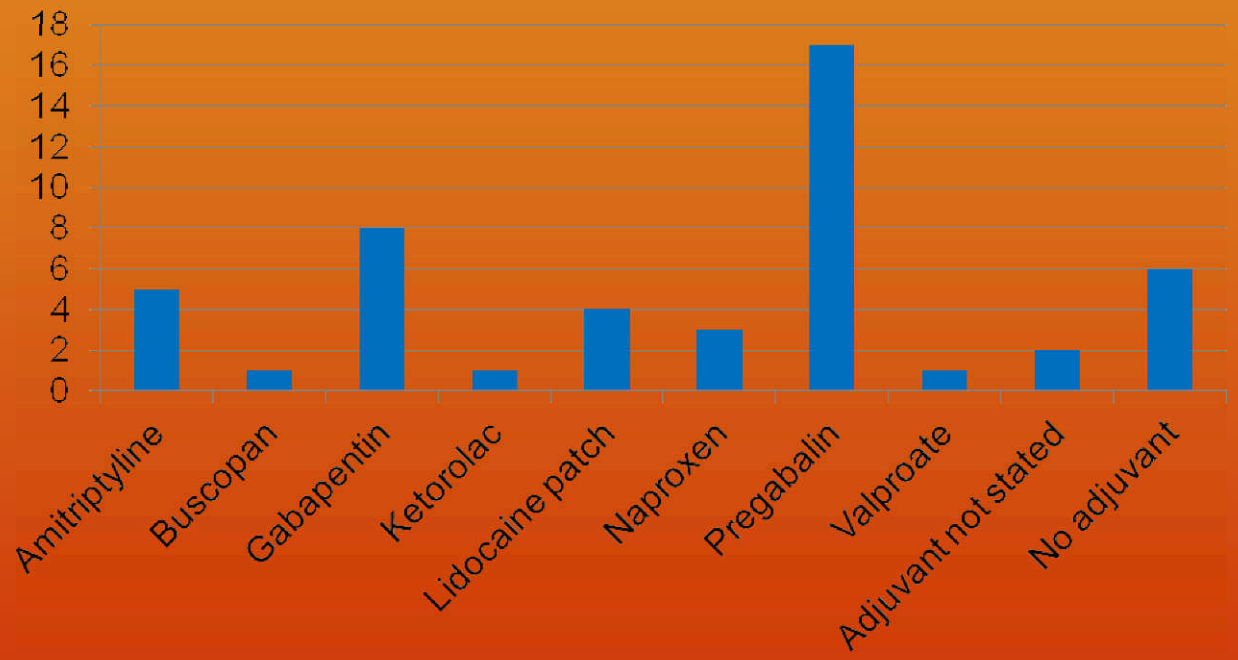


Were any side effects observed?

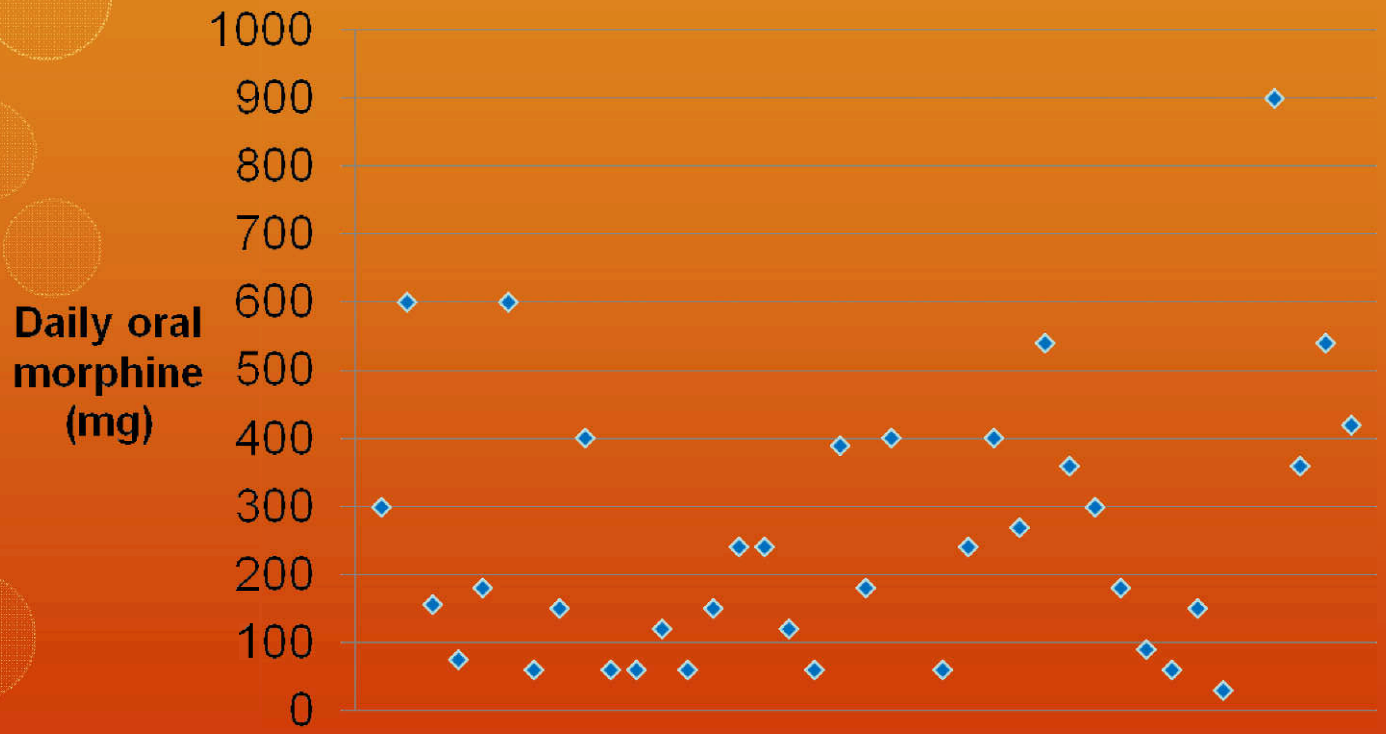




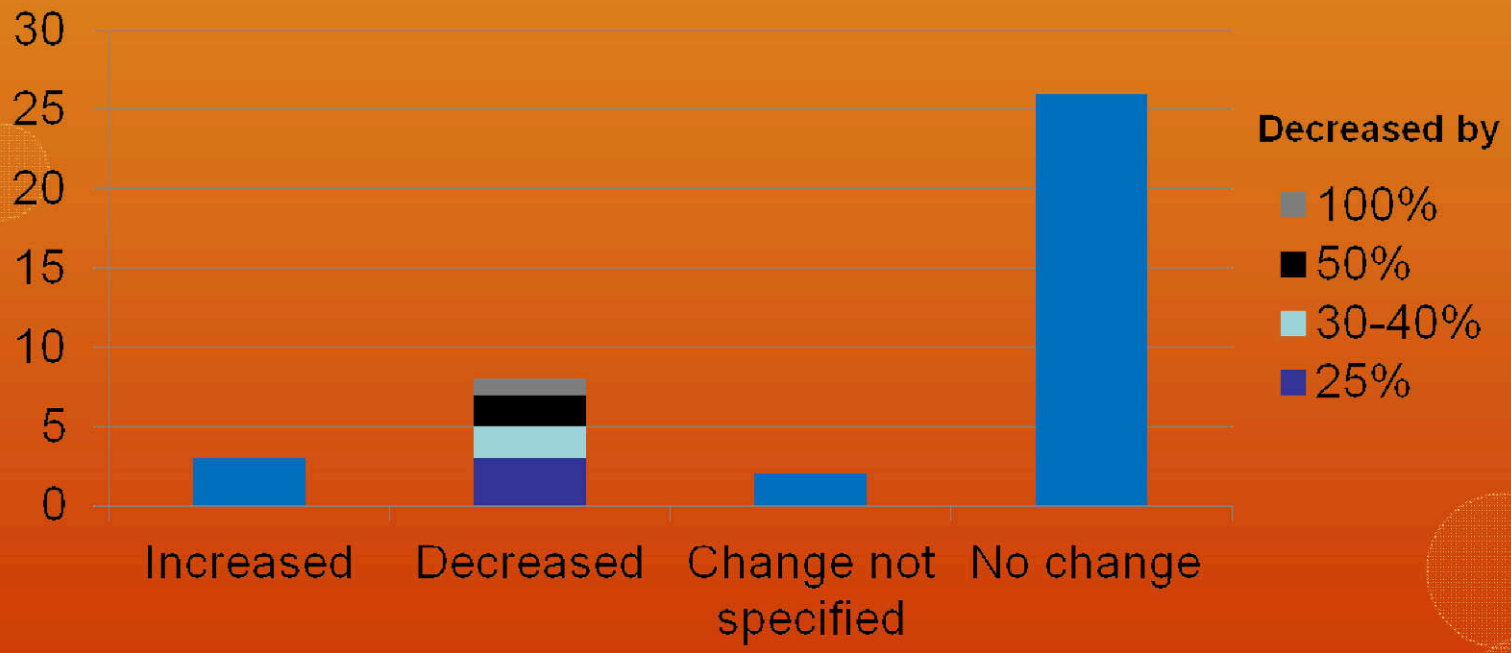
What adjuvants were used prior to starting ketamine?



How much opioid was the patient on prior to starting ketamine?



Did the patient's opioid dose change following commencement of ketamine?



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