

Neuropathic Pain Peripheral Neuropathy Workshop

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RPAH

Pain Management Centre

*Alliance For Improving the
MANAGEMENT of PAIN
2014*



CLASSIFICATION OF NEUROPATHY

- Disease process involving cranial or peripheral nerve
- Sensory, motor and / or autonomic fibres
- Mononeuropathy
 - single nerve
- Mononeuritis multiplex
 - multiple discrete nerves
- Polyneuropathy
 - generalised and symmetrical
- Polyradiculopathy

SYMMETRICAL POLYNEUROPATHY

- Most common form of PN
 - Stocking sensory loss + distal weakness
 - Loss of ankle jerks
 - other reflexes lost with severe axonal loss (earlier in demyelination)
- **Metabolic** - diabetes, uraemia
- **Nutritional** - B12, thiamine (B6) deficiency
- **Toxic** – alcohol, drugs (statins, chemotherapy), metals (Pb)
- Connective tissue disorders, vasculitis
- Malignancy, paraprotein, amyloid
- Hereditary (HMSN, HSN) and infection (HIV, Lyme)

MONONEUROPATHIES

- Sensory loss and weakness in territory of individual nerve
 - Entrapment compression
 - median nerve at the wrist
 - ulnar nerve at the elbow
 - common peroneal nerve at the fibular head
- Trauma
- Diabetes
- Leprosy and Sarcoid
- Vasculitis
- Hereditary sensitivity to pressure palsies
- Multifocal motor neuropathies

CASE 1 - HISTORY

- 64 yo man
- NIDDM Dx 2002 - HbA1c 8.8%
 - Diamicon MR
- 5 month history of increasing paraesthesia and numbness of both feet
 - walking on “cotton –wool”
 - unsteady when walks
 - no pain

CASE 1 - EXAMINATION

- Wide based gait
- Reduced sensation in stocking distribution to mid-shin
- Absent vibration sense to ankles
- Absent ankle reflexes
- Reduced knee reflexes

CASE 1- DIAGNOSIS ?

- **Diabetic Peripheral Neuropathy**
- International Consensus Meeting defined diabetic peripheral neuropathy as:
 - “the presence of symptoms and / or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”

CASE 1–FURTHER INVESTIGATIONS ?



INVESTIGATIONS - ELECTROPHYSIOLOGY

- Study of function of nerves and muscle
 - Considered an extension of the clinical exam
 - Performed by experienced physician
- Uses
 - peripheral nerve dysfunction
 - large fibre peripheral neuropathy
 - radiculopathies
 - plexopathies

STUDIES

- **Sensory**

- Median / Ulnar / Sural

- **Motor**

- Median- APB / Ulnar – ADM

- Peroneal-EDB / Tibial-AHB

- **F waves**

- Median / Ulnar / Tibial / Peroneal

SENSORY NERVE CONDUCTION STUDIES

- Stimulate and record from nerve
- Sensory action potential amplitude
 - normal if lesion proximal to dorsal root ganglion as axon remains intact with proximal lesions - nerve root compression
- Sensory conduction velocity
 - need only record from a single point

MOTOR NERVE CONDUCTION STUDIES

- Stimulate nerve and record compound muscle action potential amplitude (CMAP) from muscle
- CMAP from proximal and distal sites
 - conduction block
- Distal motor latency
- Latency from 2 sites gives motor conduction velocity

NORMAL RESULTS

- **Upper limb**

- Median DML <4.0ms / Ulnar DML <3.0ms
- SNAP >5uV
- CMAP >5mV
- Conduction velocities >50m/s

- **Lower limb**

- Peroneal and Tibial DML <6.0ms
- Sural SNAP >5uV
- Peroneal CMAP >2mV / Tibial CMAP >5mV
- Conduction velocities >40m/s

CASE 1 – NERVE CONDUCTION

- Moderate - severe generalised sensori-motor peripheral neuropathy
 - Absent sural sensory response
 - Marked reduction peroneal and tibial motor amplitudes (0.5mV)
 - Slowing of peroneal and tibial motor conduction velocities (36 m/s)

AXONAL LOSS

- If mild, NCS normal, esp. if only involving small fibres
- Absent or low amplitude SNAP's
- Low amplitude CMAP's
- Slowing of motor and sensory CV's
 - low but $>40\text{ms}$ in UL
 - low but $>32\text{ms}$ in LL
 - fast conducting fibres survive even when 75% of axons have died)

DEMYELINATION

- Normal SNAP's
- Prolongation of DML's (>50% normal)
- Normal CMAP's distal to block
- Reduced CMAP's proximal to block
- Slowed motor CV across block
 - <80% if CMAP amplitude >80% ie UL <40m/s
 - <70% if CMAP amplitude <80%
- Absent or prolonged F waves

OTHER INVESTIGATIONS – PATHOLOGY ??

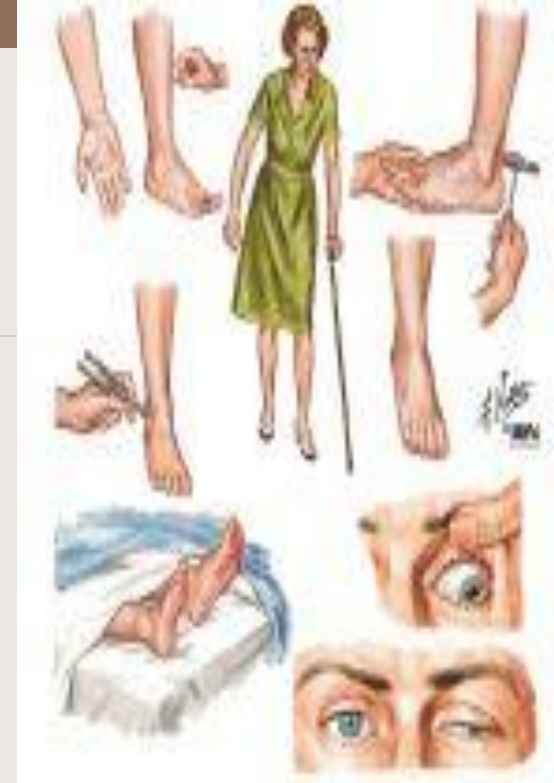
- FBC ESR
- Vitamin B12 Folate Fe Studies
- Fasting glucose (2 hr GTT) HbA1c
- EUC LFT
- ANA ENA Ds DNA
- Rh factor ANCA CRP
- Pb level TFT VDRL
- EPG IEPG
- Anti-GM1 Anti-GQ1b Anti-MAG

CASE 1 - INVESTIGATIONS

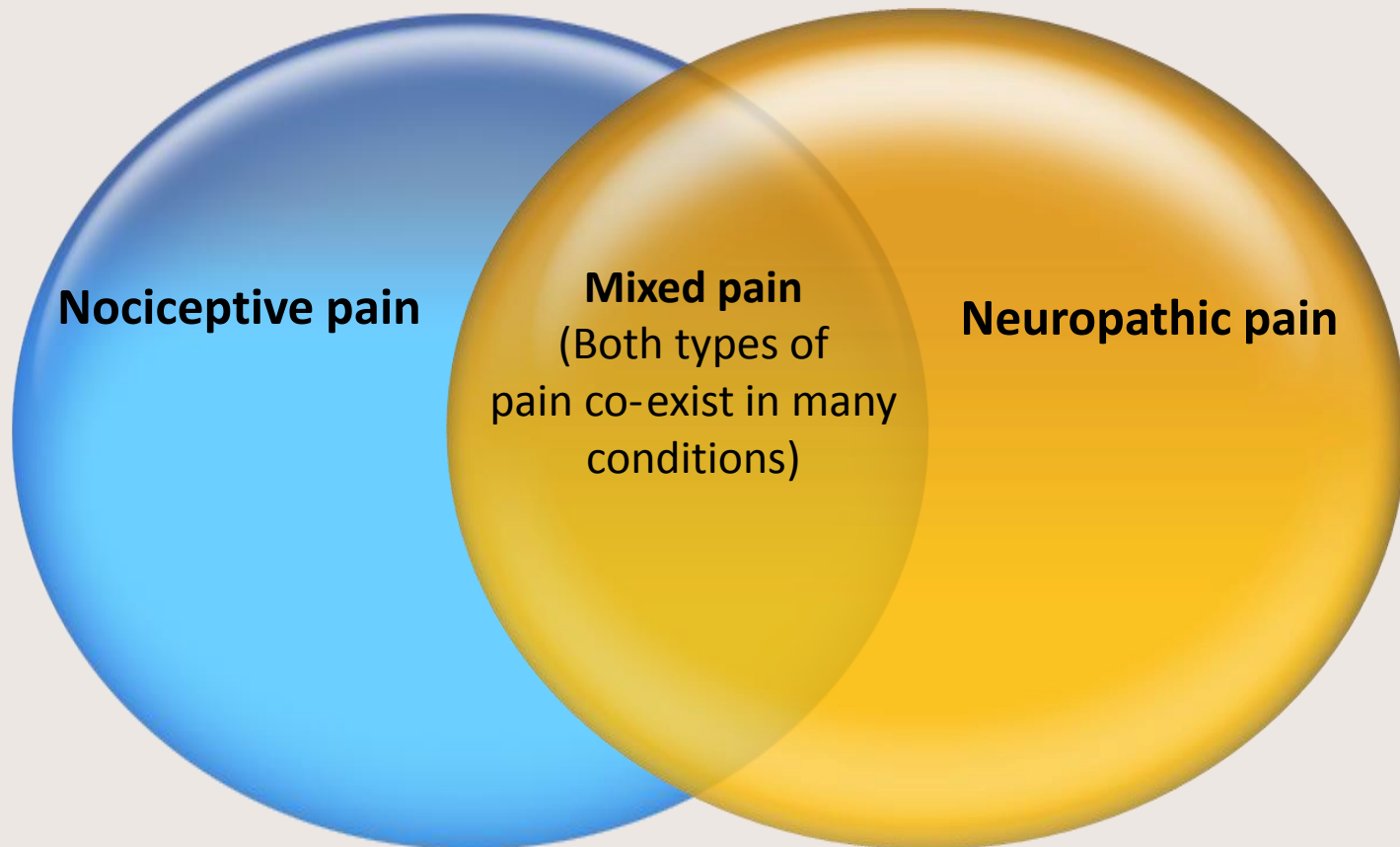
- Anaemia (Hb 94) with rouleaux formation ++
- ESR (89)
- Urea 22.8 Creatinine 310 HbA1c 6.0%
- Paraprotein 16g/L of IgG Kappa
- Subsequent Ix –
 - Urinary Bence Jones proteinuria
 - Bone marrow biopsy
 - Plasma cells >10%
- **Dx: Multiple Myeloma**

PN SYMPTOMS

- Numbness or reduced sensation
- Tingling or paraesthesia
- Neuropathic pain
 - burning sensation
 - sharp, shooting, lacerating pain
- Allodynia
 - pain to non-painful stimulus
- Hyperalgesia
 - increased pain to painful stimulus



TYPES OF PAIN



BURNING

CRAWLING

STABBING

SHOCKING

FREEZING

CASE 2 - HISTORY

- 45 year old lady
- 6 month history of:
 - Paraesthesia and tingling of both feet
 - Increased sensitivity to touch, esp. bed covers
 - Occasional burning sensation
 - Symptoms worse at night and wake her
 - Associated restless legs – 1 hour to get to sleep

CASE 2 - EXAMINATION

- Weight 60 kg
- Steady gait
- Increased sensitivity to touch to mid-shin
- Normal vibration sense and 10g microfilament
- Ankle reflexes present
- Sleep study
 - Mild restless legs
- Bloods including 2 hour glucose tolerance test
 - Normal

CASE 2 - NERVE CONDUCTION STUDIES

- NCS in India – Normal
- NCS at North Shore Hospital – Normal
- Repeat NCS - Normal
 - Sural sensory amplitude - 15-17uV
 - Peroneal motor amplitude - 7.0mV
 - Tibial motor amplitude - 11.0 mV
 - Sensory and motor conduction velocity >40m/s

CASE 2 - DIAGNOSIS ?



SMALL FIBRE NEUROPATHY

- Pain in the absence of objective signs
- Normal conventional nerve conduction studies
 - measures large nerve fibre function

CASE 2 – OTHER INVESTIGATIONS

- Punch skin biopsies
 - 3mm punch, 10cm above lateral malleolus
 - Reduced intradermal nerve fibre density
- Quantitative sensory testing (QST)
 - Non-invasive assessment of sensory perception
 - Small nerves - pain and temperature
 - Cold and heat pain thresholds
 - Large nerves – vibration threshold

CASE 2 - SMALL FIBRE NEUROPATHY

- Had previously tried
 - Amitriptyline up to 50mg nocte
 - Gabapentin 600 mg tds
 - Tegretol CR 400mg twice a day

CASE 2 – FURTHER TREATMENT ?

- **Pregabalin**

- Increased dose to 150mg bd
- Improved pain by 10-20%

- **Burning feet persists**

- Extended to ankles, worse at night
- Unable to continue to work

- **Next Option ?????**

CASE 2 – FURTHER TREATMENT ?

- **Tramadol SR** up to 200 mg bd
 - Improved pain by 10-20%
- **Norspan patch**, up to 20 mg weekly
 - Improved pain by 10-20%
 - Ceased due to constipation
- **Oxycontin** up to 20 mg bd
 - Improved 10-20%
 - Constipation
 - Targin not considered as improvement minimal

CASE 2 - FURTHER TREATMENT ??

- **Clonazepam** commenced 0.25mg nocte
 - Improved pain, esp. burning – 80%
 - Improved sleep
 - Feels well
 - Back to work

PREDOMINANTLY SMALL FIBRE NEUROPATHIES

- Diabetes
- Alcohol
- Amyloid
- Paraproteineamia
- Malignancy
- Radiation

PHARMACOTHERAPY

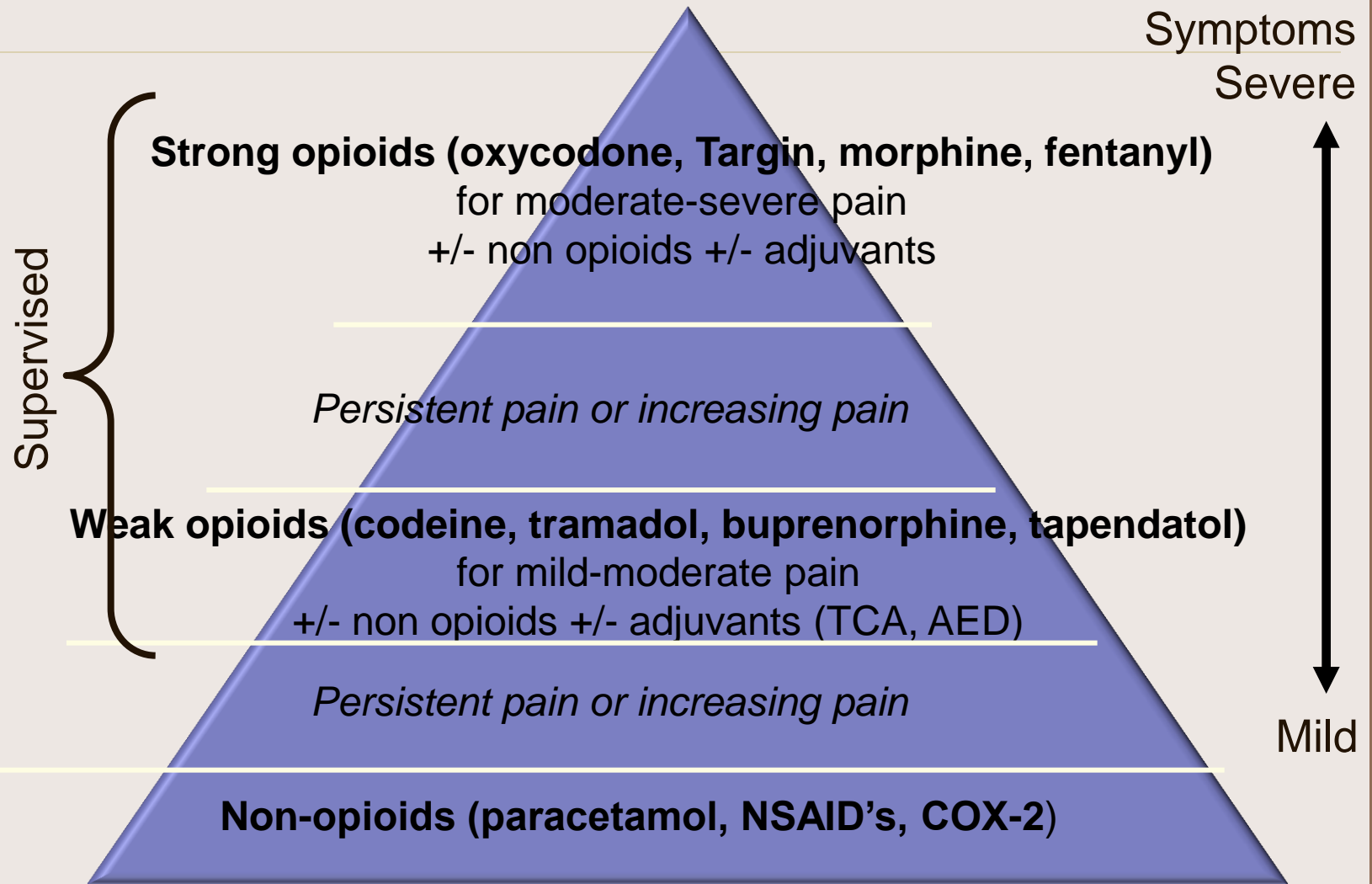


- Generally involves use of anti-convulsants and / or anti-depressants
- “Even with the current generation of drugs, effective analgesia is achieved in less than half of this population” (Sindrup 1999)

NEUROPATHIC PAIN THERAPIES - 2014

- Carbamazepine (NNT to obtain 50% relief - 1.7)
- Valproate, Phenytoin, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine
- Pregabalin, Levetiracetam, Tiagabine
- Lacosamide (Vimpat), Zonisamide
- Clonazepam
- Amitriptyline, Nortriptyline, Imipramine
- Duloxetine
- Opioids – Tramadol, Buprenorphine, Oxycodone (Targin), Tapendatol, Morphine, Fentanyl, Hydromorphone
- Baclofen, Mexilitene, Clonidine
- Capsaicin cream, Lignocaine 5% Dermal patch
- N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine
- Botulinum Toxin
- Vitamin B12

WHO ANALGESIC LADDER



NNT'S FOR DIABETIC PERIPHERAL NEUROPATHY

- Tegretol 2.3 (CI 1.6-3.8)
- Amitriptyline 2.9 (CI 2.4 - 4)
- Gabapentin 3.8 (CI 3.5-5.7)
- Tramadol 3.8 (CI 2.8 to 6.3)
- Pregabalin 3.9 – 6.6

Cochrane report (2007)

- states that whilst Gabapentin is gaining popularity as a treatment for neuropathic pain, no clear advantage has been demonstrated over Tegretol

NNH'S FOR DIABETIC PERIPHERAL NEUROPATHY

- NNH - major harm not statistically significant for any drug compared to placebo
- NNH for minor harm were:
- Tegretol 3.7 (CI 2.4-7.8)
- Gabapentin 2.5 (CI 2.0-3.2)
- Amitriptyline 3.7 (CI 2.9-5.2)
- Pregabalin 4 – 5.0
- Opioids 4.2 (CI 3.2-5.6)
- Tramadol 8.3 (CI 5.6-17) quick and slow

CASE 3 - HISTORY

- 54 yo man
- 3 day history of sudden onset R buttock pain radiating down right leg to ankle
 - Constant throbbing and BURNING with occasional shooting pain
 - Pain frequently waking him at night
 - Tried Ibuprofen and Voltaren with no relief
- Similar pain Nov 2008
 - CT disc bulge L4/5 with possible compression of right L5 nerve root
- Examination
 - Weakness right great toe dorsiflexion
 - Absent right ankle reflex
 - Reduced sensation lateral right leg

CASE 3 – DIAGNOSIS ??

- Dx – Right L5 radiculopathy
- Commenced Amitriptyline 10 mg nocte
- Changed Voltaren to Mobic 15 mg nocte
- Organised MRI lumbar spine
 - Large disc protrusion at L4/5 with compression of right L5 nerve root

CASE 3 - PROGRESS

- Sleeping better, but pain persisted
- GP added Oxycontin 10mg bd and Endone prn
- Increased Amitriptyline to 25 mg nocte
- Organised R peri-radicular block
- Pain free within 2 weeks
- Back to work and did not need block

WIND - UP

- Prolonged response to a noxious stimulus
 - dramatic increase in duration and magnitude of cell responses, but input into the spinal cord remains the same
- Activation of:
 - neurotransmitters (glutamate, substance P, NO)
 - receptors (NMDA)
 - inflammation and chemicals (neurotrophin)
 - genes (Cfos)

KETAMINE

- Ketamine
 - non-competitive NMDA antagonist
 - use limited by due side effects (hallucinations)
 - lack of oral preparation (only IV, SC and spinal).
- Oral NMDA receptor antagonists
 - Dextromethorpan
 - Amantadine and Memantine
 - Dose required e.g. for Dextromethorpan,
 - as a cough suppressant 40-80mg
 - pain 400mg / day



KETAMINE STUDY - RPAH

- Determine whether ketamine provides short and long benefits:
 - Reduce pain levels
 - Reduce opioid requirements
- Retrospective chart review of **52 patients** with chronic pain attending the RPAH Pain Clinic between 2007 and 2011
 - The assessment was based on the evaluation of a questionnaire performed over a telephone conversation

AV. DAILY KETAMINE DOSE

Description	Average daily ketamine infusion dose (mg)
Lowest	201
Highest	526
Sample Average	228

50ml Syringe

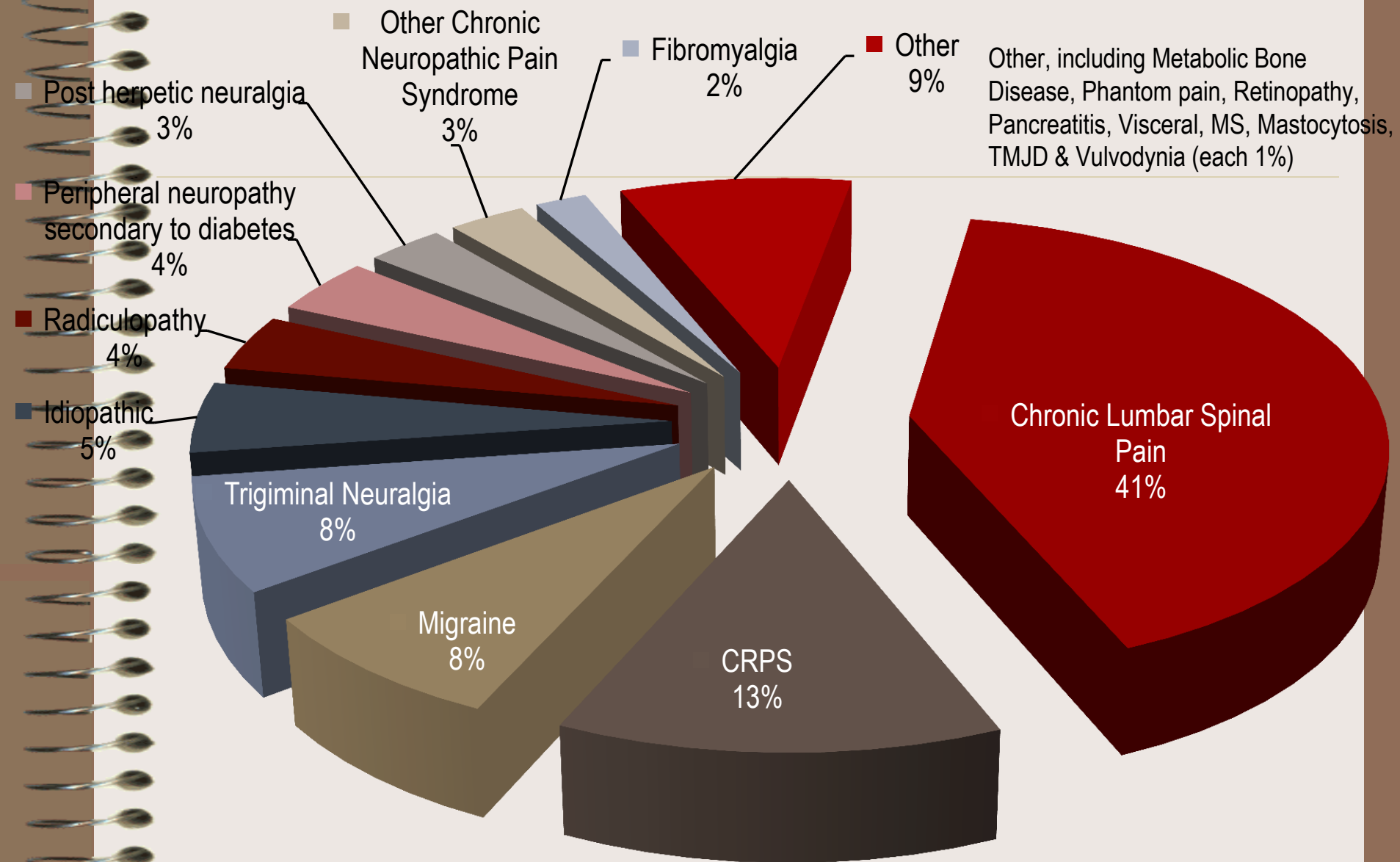
Ketamine 200mg +/- Lignocaine 2000mg (2x10x10% xylocaine)

Day 1 2ml/hr ie 8mg/hr or 192mg/day

Day 2 2.5ml/hr

Day 3 3ml/hr

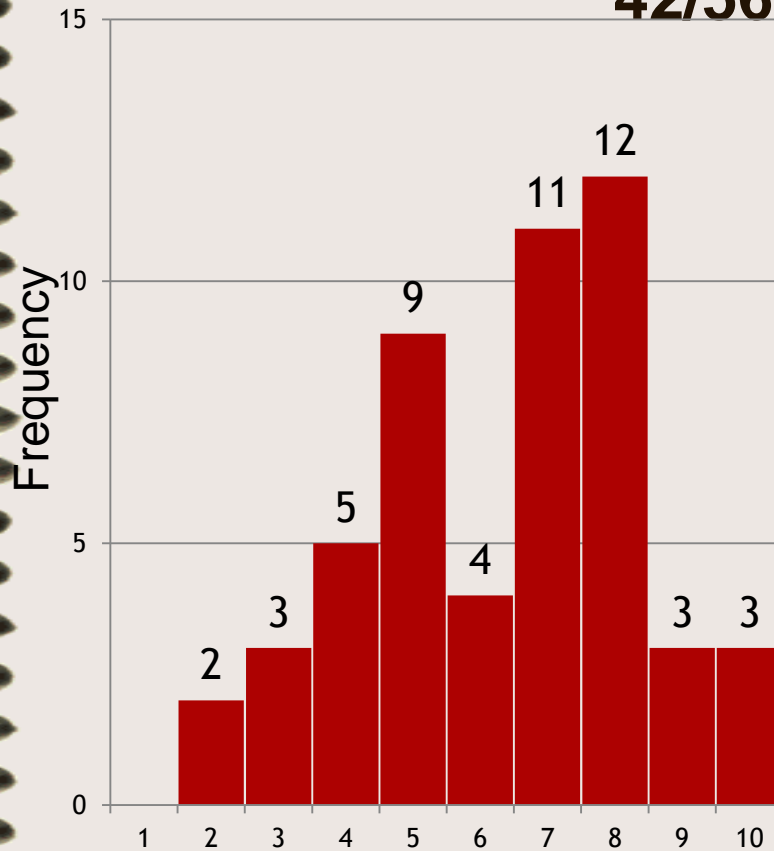
Day 4 Double Ketamine (400mg) and reduce back to 2ml/hr



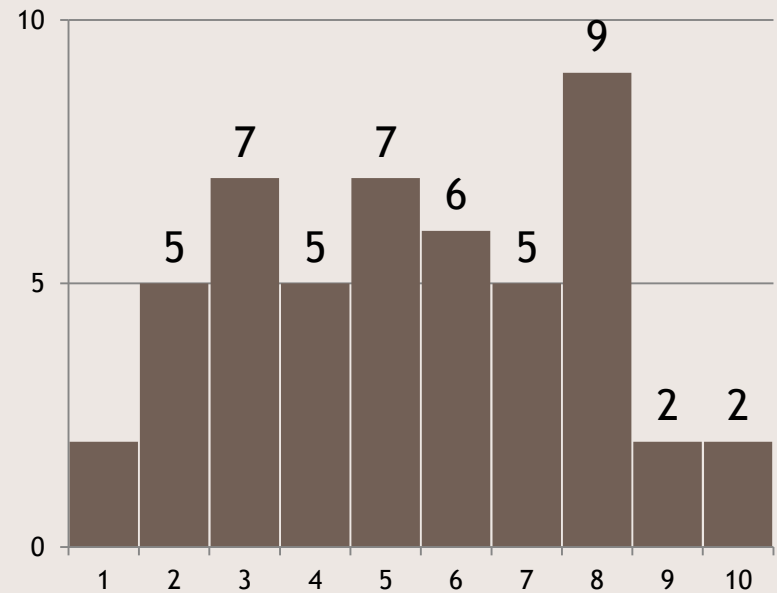
PAIN LOCATION

VAS SCORES BEFORE / AFTER KETAMINE

42/56 Improved



VAS before Ketamine (mean 6.38)



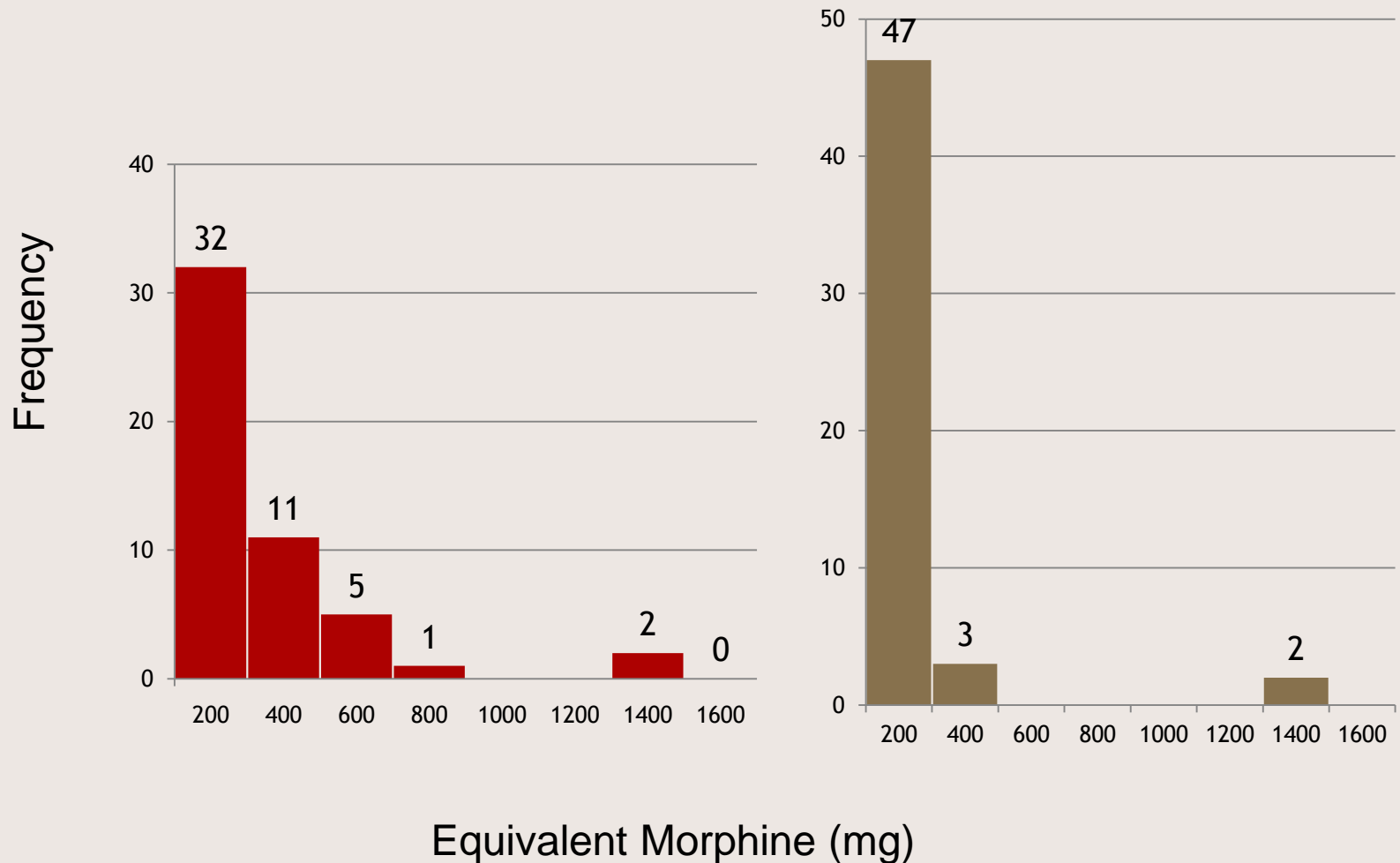
VAS after Ketamine (mean 4.60)

VAS SCORES

(BEFORE / AFTER KETAMINE)

- Significant reduction in mean pain intensity by VAS:
- **6.38 before ketamine**
- **4.60 after ketamine**
 - **($p < 0.005$)**

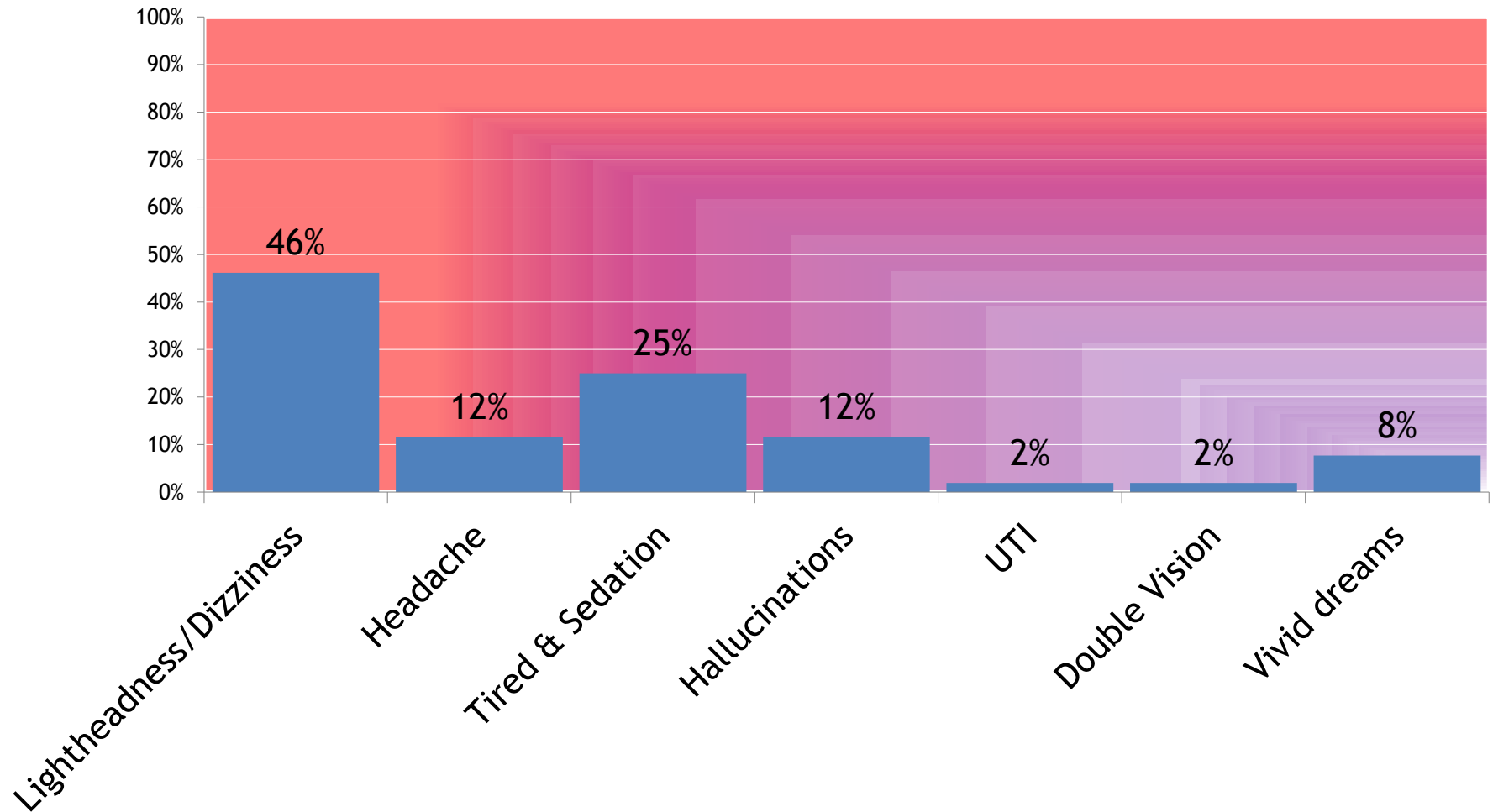
EQUIVALENT MORPHINE DOSE (BEFORE / AFTER KETAMINE)



EQUIVALENT MORPHINE DOSE BEFORE / AFTER KETAMINE

- There was significant reduction in opioid dose at the end of ketamine infusion with the mean morphine equivalent dose:
- **216 mg/day before ketamine**
- **89 mg/day after ketamine**
 - **($p < 0.005$)**

KETAMINE SIDE EFFECTS

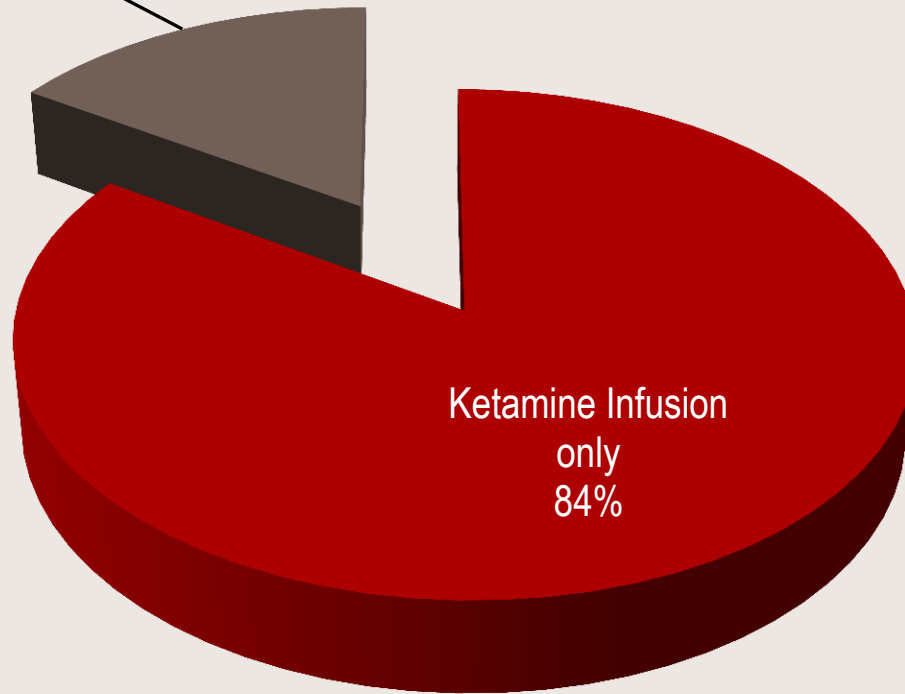


FOLLOW-UP STUDY

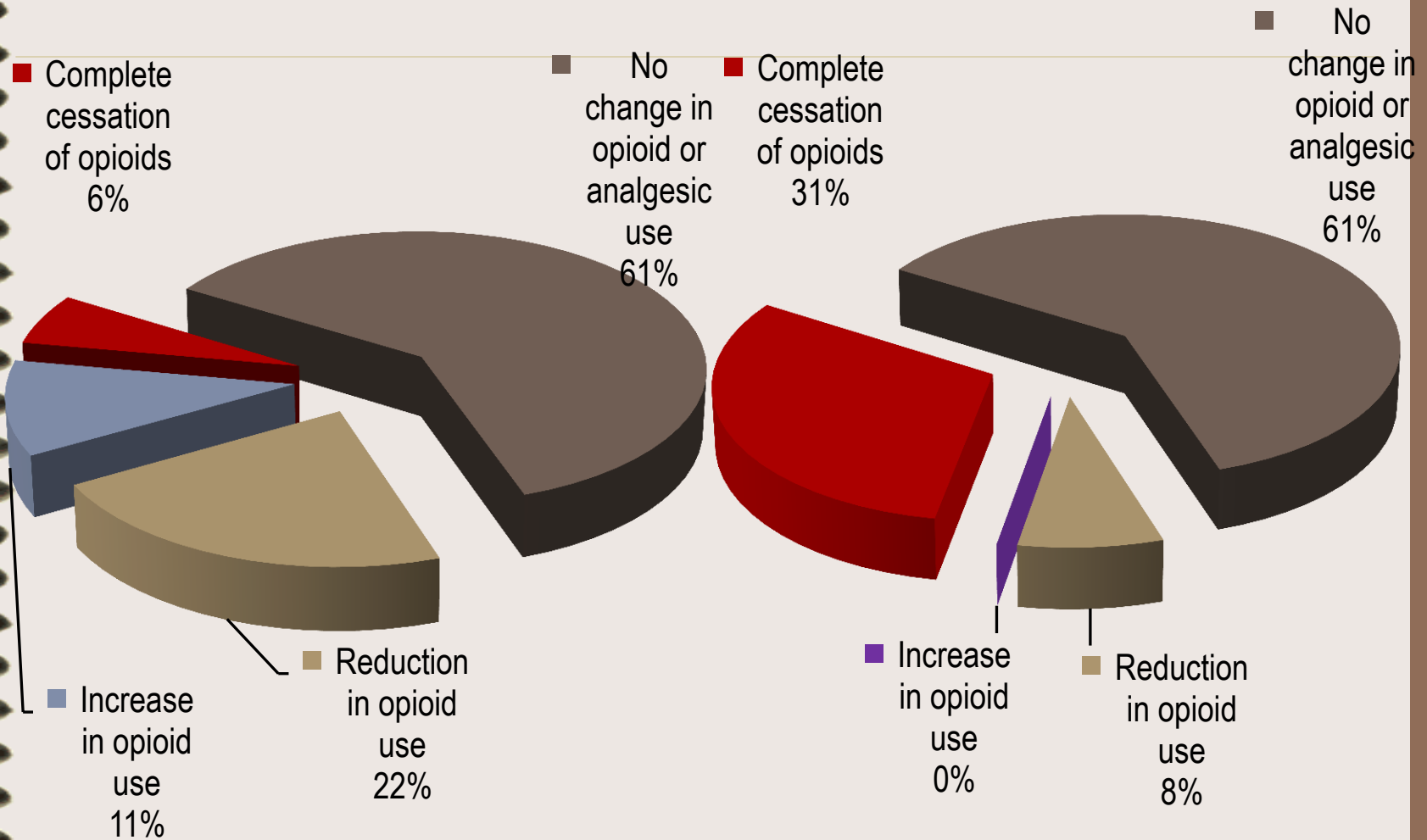
- Prospective study to evaluate long-term efficacy of sub-lingual ketamine lozenges in reducing opioid dose after a 3-7 day ketamine infusion on another **48 patients**
 - Oral or sub-lingual ketamine formulations are not currently commercially available in Australia. They have to be manufactured in hospital or compounding pharmacies
 - Studies have shown that the bioavailability of sub-lingual formulation is superior, 40% compared to 10-20% for the oral formulation
- **Dose 50mg bd increasing if required to 100mg tds**

KETAMINE INFUSION VS KETAMINE INFUSION + LOZENGES

Ketamine infusion &
Lozenges after
discharge
16%



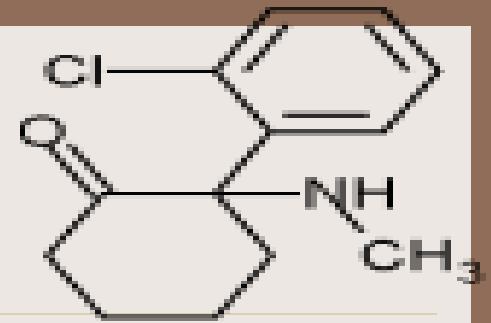
EFFECT OF KETAMINE INFUSION



NO LOZENGES

LOZENGES

CASE 4 - HISTORY



- 52yo Registered Nurse
 - Right TN Dx 1997
 - Lacinating pain in 2nd and 3rd division
 - Responded well to Tegretol and Epilim
 - Developed drug induced hepatitis
 - Microvascular decompression 1998
 - Pain free for next 4-5 years (normal facial sensation)
- Dec 2003, pain recurred
 - Commenced on Gabapentin – no response
 - 2nd microvascular decompression Aug 2004
 - No evidence of vascular compression, nerve “pinched”
 - Pain free for 3 months then recurred

CASE 4 - PROGRESS

- R facial pain in all divisions of V nerve
 - Sharp, shooting, knife-like lasting for seconds
 - Attacks of pain brought on by touching face, chewing, talking, smiling, blinking, blowing nose
 - Increased sensitivity to touch over face
- Canberra hospital in Dec 2004
 - 5 day Lignocaine infusion revealed pain but recurred once infusion ceased
- Subsequently tried:
 - Endone, MS Contin, Baclofen, Mexilitine
 - Stereotactic radiotherapy in March 2005

CASE 4 - TREATMENT

- Initial Consultation:
 - Was on Gabapentin 600 mg and Lamotrigine 150 mg 6 times a day
- Admitted to RPAH in February 2006
 - Ketamine and Lignocaine infusion
 - Improved pain within 24 hours
 - Reduced Gabapentin and Lamotrigine within 3 days
 - 50% to 3 times a day
- Discharged home pain free
 - Ketamine lozenges 25 mg three times a day

CASE 4 – FOLLOW-UP

- Follow up March 2006 (4 weeks post)
 - Remained pain free and now able to touch face, rub cream, blow nose (unable to do for over 2 years)
 - Ceased Gabapentin and reduced Lamotrigine to 100mg tds
 - Feels less drowsy and has more energy
- July 2006
 - Pain very well controlled – ceased Lamotrigine
 - Wearing make-up and no pain with wind blowing on face
- December 2006 – (nearly 12 months post infusion)
 - Leading a completely normal life, without pain worry
 - Ketamine 25 mg three times a day only

CASE 4 – FOLLOW-UP

- November 2007
 - Reduced Ketamine to 25 mg twice a day and no episodes of pain
- December 2008
 - Ceased Ketamine Jan 2008
 - Accidentally hit face 2 months later – recurrence of pain
 - 4-5 episodes only in 6 months, lasting seconds when washes face in shower
- January 2012
 - Recurrence of pain with pain persisting despite recommencing Ketamine lozenges
 - **Readmitted for Ketamine Infusion then lozenges**
 - Pain free again – last review Jan 2014

STUDY SUMMARY

- The ketamine infusion was tolerated well with only 1 patient prematurely ceasing the infusion
 - 46% of patients experienced light-headness or dizziness, but did not need to discontinue the infusion
- Overall reduction in opioid use after Ketamine infusion was **39%**
 - When Ketamine lozenges were given after the infusion, **31% were able to completely cease opioids** compared to **6%** without lozenges
- Reduction in pain (VAS) in **42/56 patients** with only 5 patients noticing no change in the VAS by the end of the infusion

STUDY SUMMARY

- Provides strong evidence that a 3-7 day intravenous ketamine infusion has the potential to:
 - Reduce VAS
 - Reduce equivalent morphine doses in the short and long-term, even in chronic pain patients who have responded poorly to treatment in the past.
- When Ketamine lozenges are given after the infusion, **long-term benefits are sustained with reduced opioid use and pain control**

CONCLUSION

- Neuropathic pain is common, under-reported, under-diagnosed and under-treated
- A simple, stepwise approach to diagnosis may help differentiate between neuropathic and nociceptive pain:
 - Listen to the patient's pain description
 - Locate a potential nerve lesion/dysfunction, if possible
 - Look for neurological symptoms, such as sensory deficits

CONCLUSION

- Neuropathic pain responds poorly to conventional analgesia
 - First-line treatments include:
 - TCAs (amitriptyline)
 - Alpha 2-delta ligands (pregabalin)
 - SNRIs (duloxetine)
 - Second-line treatments include:
 - Opioids

CONCLUSION

- Pain can exist without objective signs
- Step-wise approach to medications
- Start small and increase slowly
- Use medications to maximum tolerated potential
- Combination therapy often required
 - different pain mechanisms
- Realistic goal is **PAIN MANAGEMENT** rather than resolution