



Trigeminal Neuralgia Medical Management: Why Medication is not working

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RPAH Pain Management Centre*



WHY MEDICATIONS FAIL?

1. Wrong Diagnosis
2. Wrong Medication (Nociceptive vs Neuropathic)
3. Pharmacokinetics
4. Compliance
5. Drug tolerance
6. Wind-up
7. Psychological Influence

WHY MEDICATIONS FAIL?

1. Wrong Diagnosis

NOT ALL FACIAL PAIN IS TN

- **Multiple sclerosis** (plaques at root entry zone)
 - 2% of MS patients have TN
 - 18% with bilateral TN have MS
- **Intracranial tumour**
 - 1% incidence
 - Pain more constant
 - Numbness present
 - Posterior fossa meningioma or acoustic neuroma
- **Herpes Zoster – (Post-Herpetic Neuralgia)**
 - Constant pain, vesicles and crusting follow

REFERRED PAIN

- **Occipital Neuralgia**
 - Sharp pain, occipitally and radiating frontally
- **Frontal and Maxillary sinusitis**
 - Pain referred to V1 / V2 and tenderness
- **Costen's syndrome (TMJ dysfunction)**
 - Pain to lower jaw and temple on chewing only
- **Nasopharyngeal malignancy**
- **Glaucoma**
 - Pain referred to temple
- **Dental caries** (peri-apical abscess, wisdom tooth)
 - Pain evoked by hot or cold fluids or food

Mr AW

- 18 yo
- Diagnosed with TN
 - 3 year history of severe L retro-orbital pain
 - Constant sharp, stabbing pain
 - Glandular fever 6 months prior
 - MRI - normal
- Epilim 1000 mg bd
 - Relieved pain
 - SE's – drowsiness, tiredness and weight gain
- Very tender over greater occipital nerve region

Mr AW

- **Occipital Neuralgia – Not TN**
 - Irritation of GON
 - Trauma
 - Tight muscles
 - Degenerative Arthritis
 - Viral
- **GON block – LA only**
 - Relieved pain completely for 4 weeks
 - Recurred, but not as constant or severe
- **Repeat block with LA and cortisone**
 - Relieved pain for 6 weeks
- **Radiofrequency of GON**
 - Pain resolved
 - Weaned off Epilim
 - Drowsy during the day settled

Cluster Headache

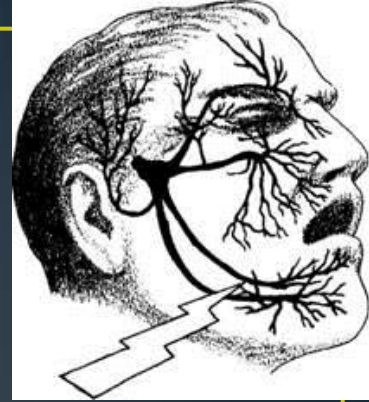


- V distribution (eye and frontalis)
 - 20-40 year old, mainly males
 - Deep, boring and intense with no precipitating trigger
 - 5 attacks of unilateral orbital or temporal pain
 - Lasting 15 min to 3 hours daily for weeks to months
- Conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis, miosis and sweating
- **Episodic Paroxysmal Hemicrania (Indocid)**
 - Pain lasting 15 mins
 - Occurring 6-30 times per day for 1-5 months
 - Remission for months to years

SUNCT and SUNA

- **Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing**
 - Most common in men over 50
 - Bursts of pain usually around the eye,
 - Lasting 5 seconds to less than 5 minutes (5 / hr)
 - Burning, stabbing, throbbing
- Autonomic features
 - SUNCT - Watery, reddish eyes
 - SUNA - Nasal congestion, runny nose

Trigeminal Neuropathy



- **Trigeminal sensory neuropathy**
 - Persistent sensory loss and pain
 - Trophic ulceration of the nose
 - May be unilateral or bilateral
 - Vasculitis
 - Scleroderma, SLE, Sjoren's, RA
- **Chronic trigeminal neuropathic pain**
 - Constant pain – No trigger
 - May occur after removal of impacted teeth, facial #’s

Mr A MD

- 82 yo
- Upper molar extraction and root canal therapy
 - Only 2/3 root removed
- 15 year history of L mandibular pain
- **Constant** dull ache and burning sensation
 - Inside mouth and side of tongue
- Frequent sharp, shooting pain
 - Triggered by talking, chewing and eating
- Normal facial sensation and power
- **Chronic Trigeminal Neuropathic Pain Syndrome**

Mr A MD

- Dx - TN 1992
 - Tegretol – allergy
 - Clonazepam – no improvement
 - Epilim - no improvement
 - Amitriptyline - no improvement
 - Phenytoin - no improvement
- Oral surgeon
 - Denture adjusted
 - Improved pain - few weeks
 - Transposition of left mental nerve
 - Improved pain – few weeks



Mr A MD

- Gabapentin – 300mg tds
 - Pain no longer constant
 - improved burning sensation 50%
 - Able to chew and eat (eat breakfast) without pain
 - Sharp shooting pain when brushes with cold water
 - Mild SE's – drowsy and unsteadiness
- Added Amitriptyline 10mg nocte
- **Pain free for 2 weeks (first time in 5-6 years)**
- Felt good, reduced Gabapentin to 100mg daily
 - Pain recurred
 - Increased dose – **PAIN FREE AGAIN**

OTHER CAUSES of FACIAL PAIN

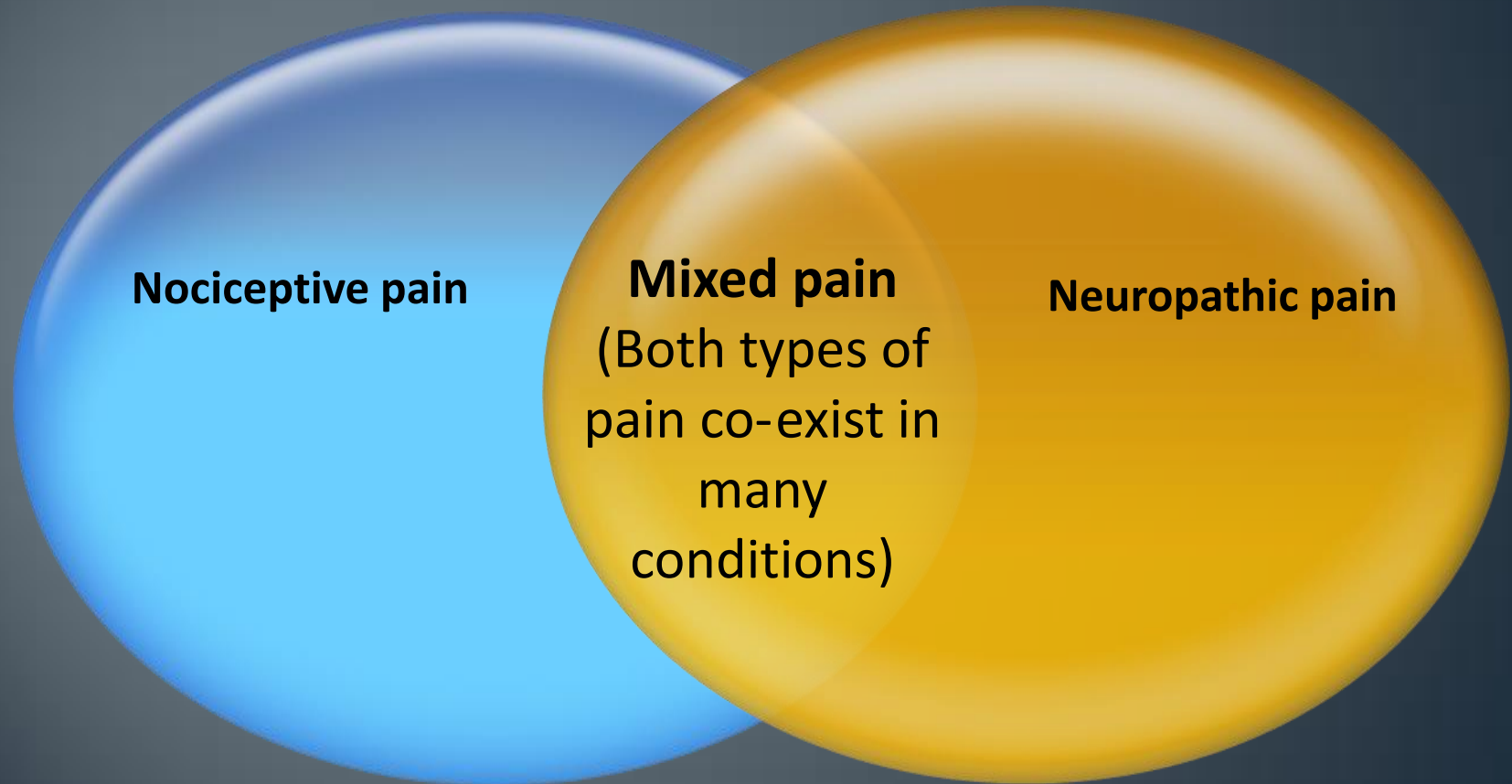


- **Sluder's sphenopalatine neuralgia**
 - Pain at the root of the nose, eye, jaws, teeth and ear
 - Reduced sensation of soft palate and taste
- **Anaesthesia dolorosa**
 - Pain in an area which is numb
 - Due to deafferenting disease or ablative procedure
 - Central pain (burning, tearing) - no trigger
- **Glossopharyngeal neuralgia**
 - Pain referred to:
 - Ear, base of the tongue and below the jaw
 - Provoked by swallowing, talking or coughing

WHY MEDICATIONS FAIL?

1. Wrong Diagnosis
2. **Wrong Medication Nociceptive vs Neuropathic**

TYPES OF PAIN



NOCICEPTIVE PAIN

“Pain caused by stimulation of somatic or visceral nociceptors by tissue damaging (noxious) stimuli”

- Dull ache
 - OA, sprained ankle
- Responds well to standard pain medications or anti-inflammatory medication

NEUROPATHIC PAIN

“Pain initiated or caused by a damage, disease or dysfunction in the nervous system, in the absence of ongoing peripheral noxious stimulus”

- Responds poorly to standard pain medication
- Persists and results in functional impairment

BURNING

CRAWLING

STABBING

SHOCKING

FREEZING

DN4 Questionnaire

Completed by physician
Differentiates neuropathic from
nociceptive pain

2 pain questions (7 items)

2 skin sensitivity tests (3 items)

Validated

>4/10 - Neuropathic

**DN4: Douleur
Neuropathique en 4
questions.
Bouhassira D, et al. 2004**

Please complete this questionnaire by
ticking one answer for each item in the four
questions below.

A "YES" score of ≥ 4 is diagnostic of
Neuropathic Pain.

Patient Name: _____
Gender: _____
DOB: _____
Date: _____
Time: _____

Interview of the patient

Yes

No

Does the pain have one or more of the following characteristics?

1. Burning
2. Painful cold
3. Electric Shocks

☐
☐
☐
☐
☐
☐

Is the pain associated with one or more of the following symptoms in the same area?

4. Tingling
5. Pins and Needles
6. Numbness
7. Itching

☐
☐
☐
☐
☐
☐
☐
☐

Examination of the patient

Yes

No

**Is the pain located in an area where the physical examination may reveal one or more
of the following characteristics?**

8. Touch Hypoaesthesia
9. Prickling Hypoaesthesia

☐
☐
☐
☐

In the painful area, can the pain be caused or increased by:

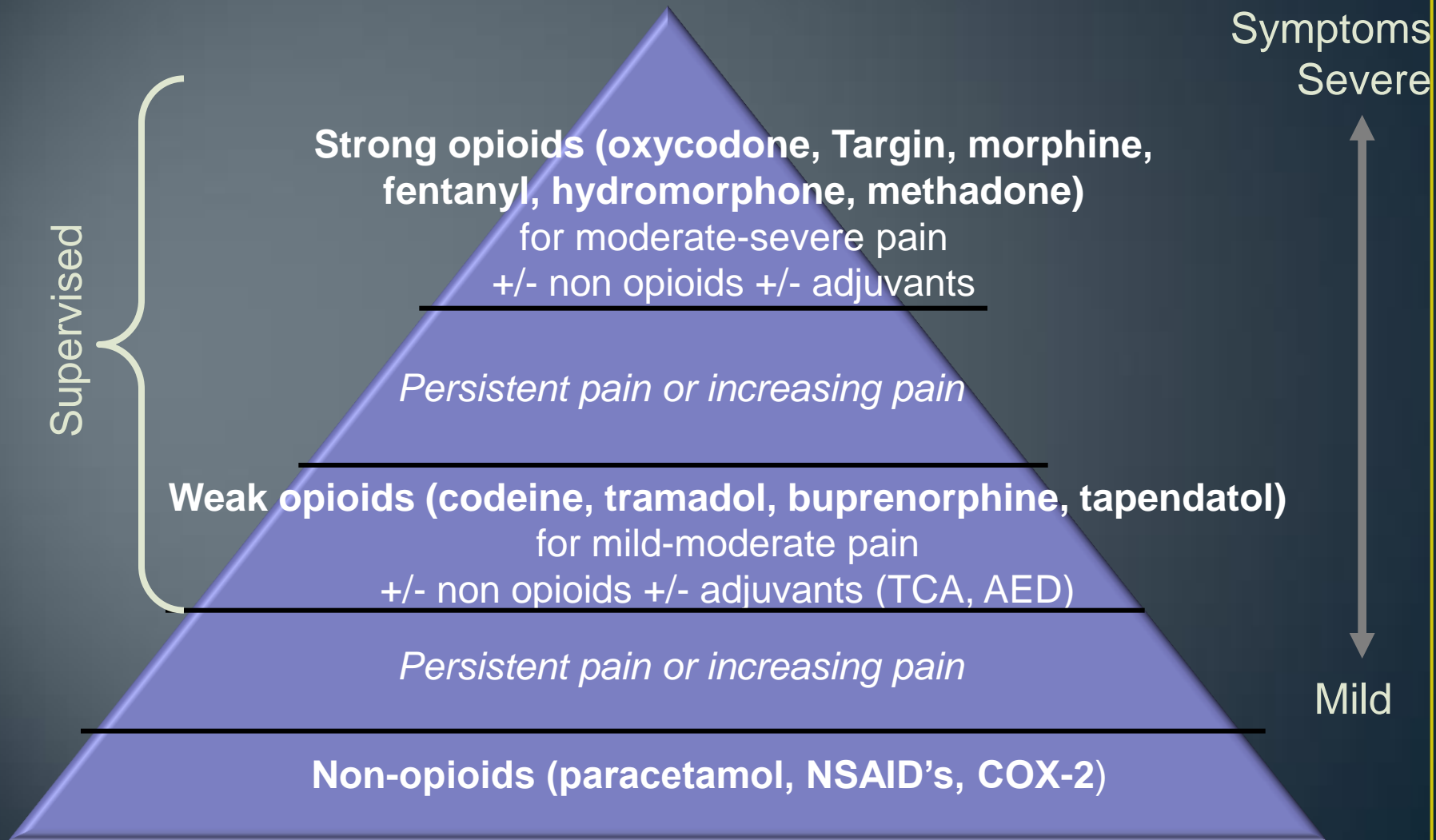
10. Brushing

☐
☐

Patient Score:

/10

WHO ANALGESIC LADDER (GENERALLY FOR NOCICEPTIVE PAIN)



PHARMACOTHERAPY

Initial Analgesic options	<ul style="list-style-type: none">• Paracetamol (1000mg qid)• Panadeine Forte (2 x 500mg/30mg qid)• Tramadol Quick Acting Capsules (50mg qid)
Pain lasting > 5 days	<ul style="list-style-type: none">• Tramadol SR (100-200 mg bd) or Duro-Tram XR (100-300mg nocte)• Tapendatol SR (50 – 200mg bd)• Buprenorphine patch (5-20 ug/hr weekly)• Oxycontin 10-20 mg bd or Targin 10/5 – 20/10 mg bd• Fentanyl patch 12-25 mcg every 3 days
Nocturnal Pain (TCA antidepressant)	<ul style="list-style-type: none">• Amitriptyline (10-25mg nocte) / Nortriptyline• Doxepin (25-50mg nocte)• Clonazepam (0.25-0.5mg nocte)
Daytime Pain (Adjuvant AED)	<ul style="list-style-type: none">• Epilim (200-400 mg bd)• Pregabalin (25-300 mg bd)• Gabapentin (100 – 600 mg tds)• Duloxetine (30-120 mg mane)

NEUROPATHIC PAIN THERAPY 2013

- 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

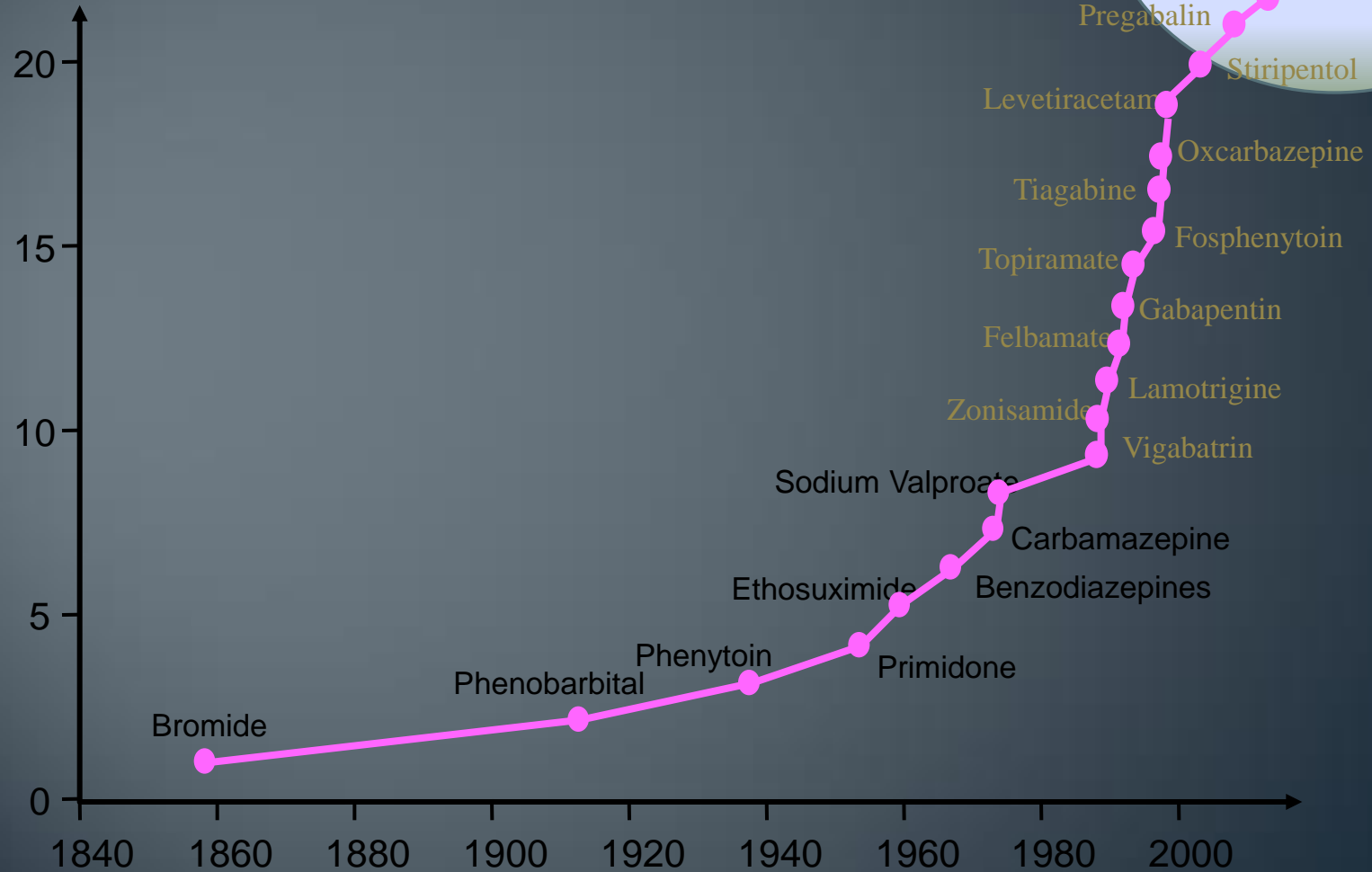
Mrs RF

- 88 yo
- TN diagnosed 30 years ago
 - Symptoms responded well to Tegretol
- Recurrence of pain
 - GP commenced Gabapentin
 - Ongoing constant burning pain
 - Intermittent sharp electric shock pain when chews and talks
 - Increased sensitivity to touch
- Trileptal 75 mg daily – bd – 150 mg bd
 - Pain free and able to chew and talk
- Weaned off Gabapentin

ANTI-CONVULSANTS

2013

Anti-convulsant drugs



Calendar year

VITAMIN B12

Wood & Aggarwal

Group	B12 Serum level (pgm/L)	Trigeminal Neuralgia patients	Other Facial Pain patients	
1	<106	0	0	
2	106-200	13	2	
3	201 - 300	18	11	
4	301 - 400	14	4	
5	401 - 450	5	2	
6	> 450	7	0	
Total		57	19	76 patients

20% were vitamin B12 deficient (<200pg/ml)
71 % had low vitamin B12 levels (200-450pg/ml)

WHY MEDICATIONS FAIL?

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2. Wrong Medication (Nociceptive vs Neuropathic)
- 3. Pharmacokinetics**

3. PHARMACOKINETICS

- TN medications are not taken like normal pain killers
 - Not to be taken only when you are in pain
- Medication levels need to build up in the blood and reach **steady state**
 - Achieved only when drug is administered at a constant rate
 - Drug elimination is equal to drug concentration
 - Prior to this, drug concentrations rise and fall with each dose
 - Attained after approx 4-5 half-lives
 - Time for amount of the drug in the body to reduce 50% - depends on clearance and volume of distribution)
- Clearance is a measure of ability to eliminate the drug
 - Influenced by disease processes and protein binding of the drug

PHARMACOKINETICS

- Wrong dosing regimen
 - Under-dosed, sub-therapeutic
 - Individualise – everyone responds to drugs differently
 - Trial and adjustment
 - Patient in control
- Continuity of delivery
 - Manage constant pain with regular medication
 - Slow release preparations (**Tegretol CR**)
 - PRN medication for breakthrough pain
 - **PAIN RELIEF NEVER**

PHARMACOKINETICS

- **Obesity**
 - Drugs distributed in fat remain longer
- **Dehydration**
 - Drugs become more concentrated – side effects
- **Gastroparesis**
 - Slows transit time through to small intestine – action delayed
- **Liver disease**
 - Lack of enzymes to break down medication – toxicity
- **Renal disease**
 - Medications filtered slower through kidney - toxicity

WHY MEDICATIONS FAIL?

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4. **Compliance**

4. COMPLIANCE

- Minimise SE's
 - Medications increased gradually
 - Constipation, drowsy, nausea, dizziness, unsteadiness
- Drug interactions
 - Food, alcohol, antacids, grapefruit juice reduce absorption
- Co-existent chronic medical conditions
 - IHD, DM
 - Body metabolises drugs less effectively
- Allergies

COMPLIANCE

- Complicated dosage schedules
 - No clear understanding of what medication is for
 - Frequent dosage – more likely to forget tablets
- False expectations
 - Instant relief - cease too soon – within days
 - If well controlled, consider weaning medication after being pain free for 3-6 months
- Financial

WHY MEDICATIONS FAIL?

1. Wrong Diagnosis
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4. Compliance
- 5. Drug tolerance**

5. DRUG TOLERANCE

- Body gets used to medication
 - Medication not as effective as before
 - Increased clearance of the drug
 - Over time need to take larger doses
 - Consider switching medication with different mechanism
 - Consider combination therapy (low doses)
- **Addiction**
 - Craving and compulsive use of drugs
 - Physical dependence as body adapts to the drug
 - Withdrawal
 - Aches, irritability, sweating, diarrhoea

ANALGESICS MAY INCREASE PAIN

- Opioids change the brain neurochemistry
 - Brain increases the number of opioid receptors
 - Body stops producing endorphins
 - Degeneration of neurones results in physical dependence on external opiates
- Long-term
 - Increases sensitivity to pain (hyperalgesia)
 - Decreases ability to tolerate pain

WHY MEDICATIONS FAIL?

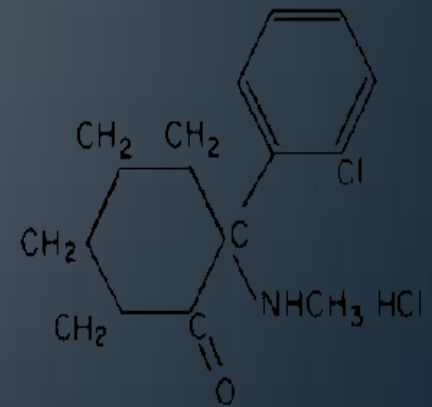
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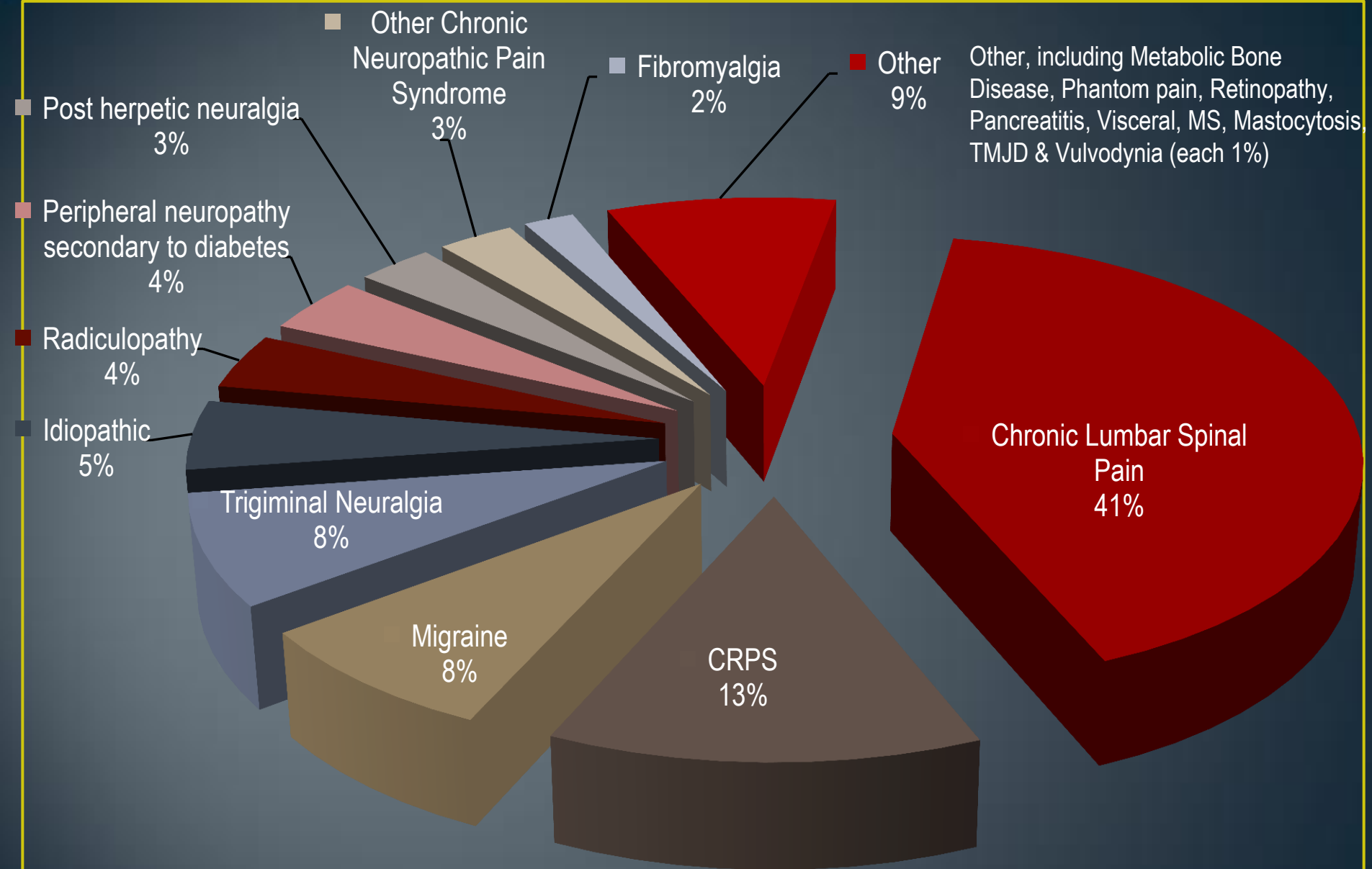
6. 'WIND UP'

- 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, sub P) and receptors (NMDA)
 - Inflammation and chemicals (neurotrophin) and genes (Cfos)
- **KETAMINE**
 - Non-competitive NMDA antagonist at dorsal horn of SC
 - Inhibits binding of excitatory glutamate to NMDA receptor
 - Blocking transmission of pain
 - Highly lipid soluble so crosses BBB rapidly

KETAMINE

- Ketamine is a non-competitive antagonist of N-Methyl-D- Aspartate (NMDA) receptor
- Acts on:
 - Kainate
 - Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
 - Gamma-aminobutyric acid (GABA) receptors
 - Inhibition of voltage gated Na(+) and K (+) channels and
 - Serotonin, dopamine re-uptake
- Antagonizing NMDA receptors
 - Improves opioid receptors sensitivity
 - Reduces opioid tolerance
 - Suppresses opioid-induced hyperalgesia





PAIN LOCATION

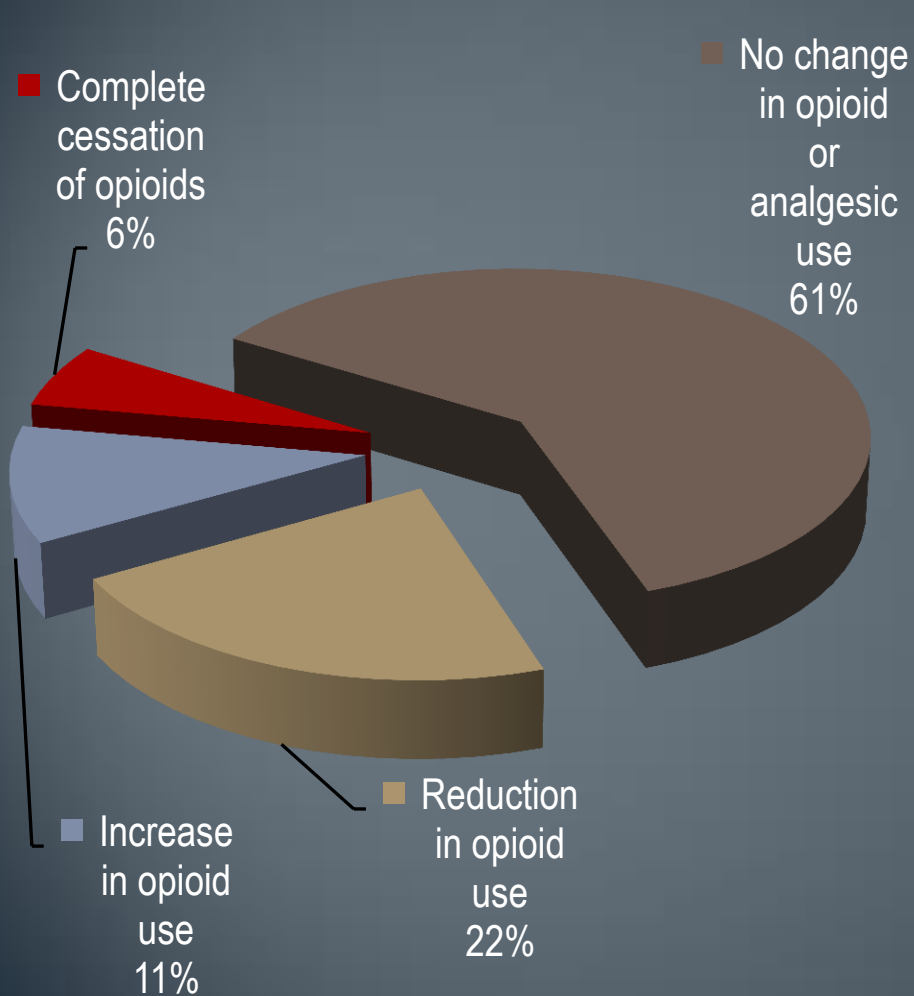
VAS SCORES (BEFORE / AFTER KETAMINE)

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

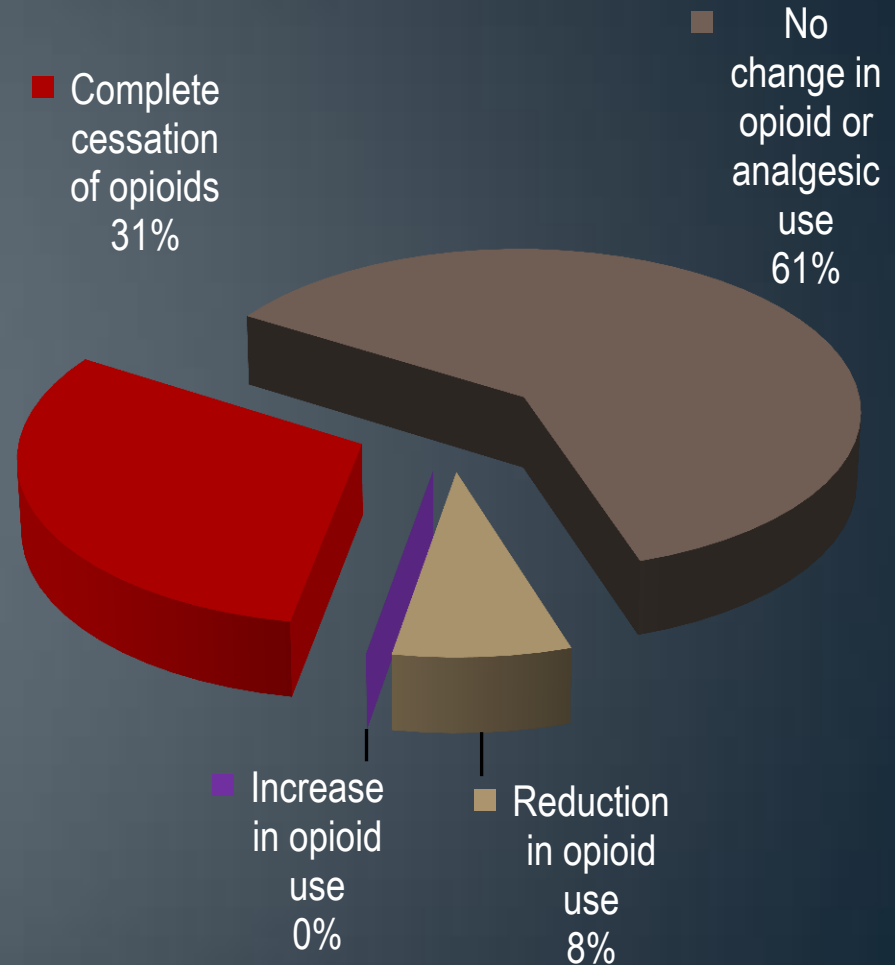
EQUIVALENT MORPHINE DOSE BEFORE / AFTER KETAMINE

- 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**
 - **($p < 0.005$)**

EFFECT OF KETAMINE INFUSION

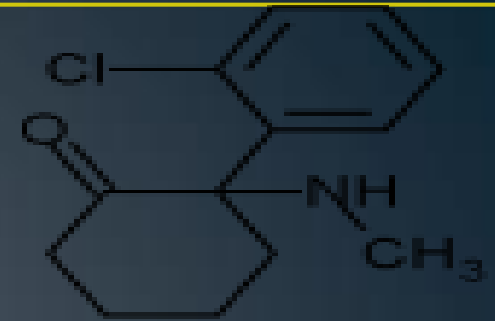


NO LOZENGES



LOZENGES

Mrs CH



- 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

Mrs CH

- 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

Mrs CH

- 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

Mrs CH

- 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

Mrs CH

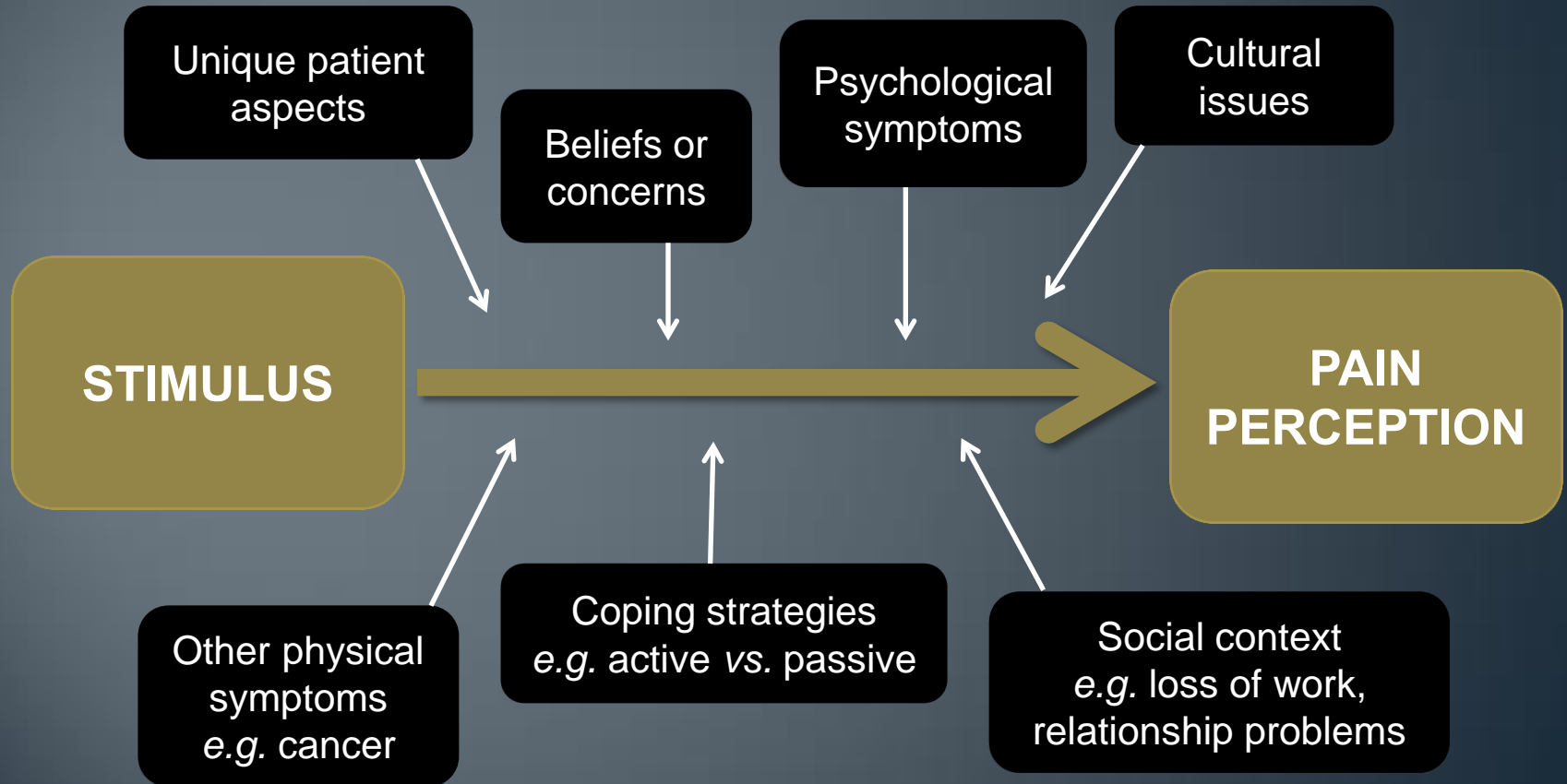
- November 2007
 - Reduced Ketamine to 25 mg twice a day and no episodes of pain
- December 2008
 - Ceased Ketamine Jan 2008
 - Accidentally hit face 2 months later – recurrence of pain
 - 4-5 episodes only in 6 months, lasting seconds when washes face in shower
- January 2012
 - Recurrence of pain with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

WHY MEDICATIONS FAIL?

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7. **Psychological Influence**

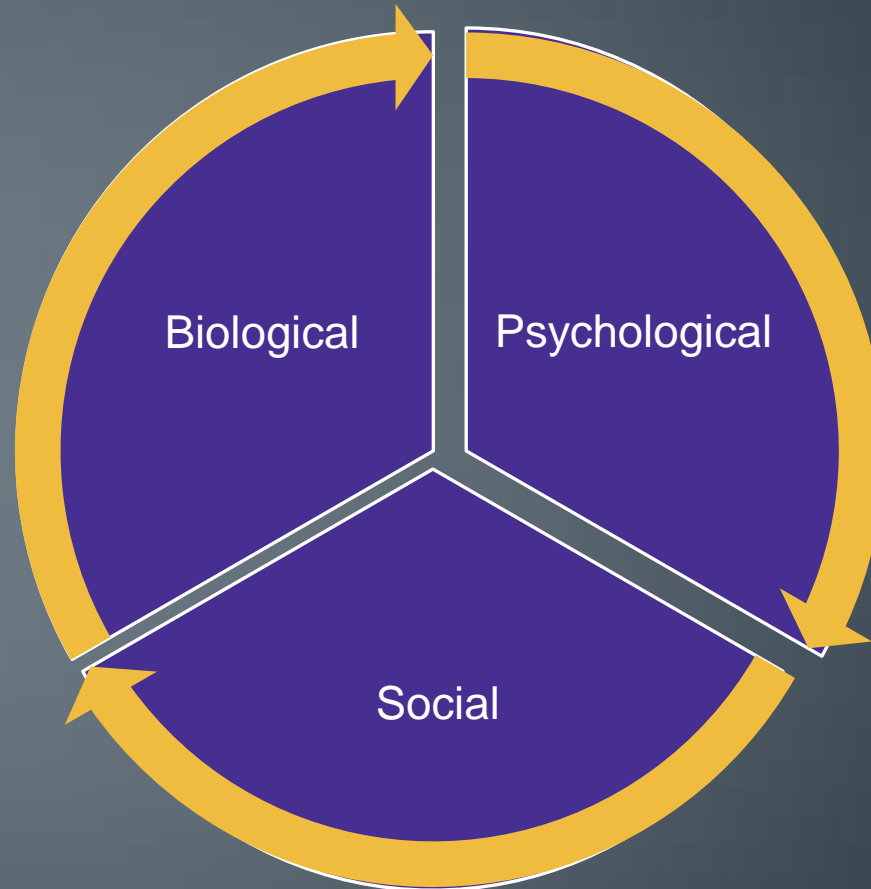
THE COMPLEXITY OF PAIN PERCEPTION

(SOCIAL AND PSYCHOLOGICAL)¹



BIOPSYCHOSOCIAL APPROACH¹

What is happening
to the body?
cause of pain



What is happening
to the person?
Impact on ADL's
Sleep
Mood
Self-esteem

What is happening in the person's world?
Impact on family, friends and work

7. PSYCHOLOGICAL INFLUENCE

- Strong relationship between chronic pain and psychological distress
- Chronic musculo-skeletal pain and depression
- Somatisation
- Anxiety
- Post-traumatic stress disorder
- Fears of physical disability
- Childhood victimisation / abuse

PSYCHOLOGICAL INFLUENCE

- Stress defined as:
 - Perceived inability to cope with an unpleasant or painful life situation
- Brain plays a primary role in identifying a situation as stressful
- Memories of past experiences and social norms result in whether we can cope with a situation
- ***Pain is stressful and stress makes pain worse***

STRESS

- **Physiological response to stress**
 - Increase in sympathetic activity
 - Release of Adrenaline and NAR
- Stimulates CRH from hypothalamus (limbic system)
 - Release of ACTH from pituitary gland
 - Cortisol from adrenal gland
 - Raised cortisol
 - Affects mood, behaviour
 - Disrupts memory and reduces serotonin synthesis
- Limbic system responds to mood and emotion

DEPRESSION AND PAIN

**Frequently coexist
(30-50% co-occurrence)¹**

- **PAIN²**

- Interferes with the recognition of depression
- Pain that is refractory to treatment may be associated with:
 - Depressive symptoms
 - Depression

**Additive adverse effect on
treatment outcomes²**

- **DEPRESSION²**

- Complicates pain management
- Is associated with:
 - Pain complaints
 - Long duration of pain
 - Risk of developing chronic pain

A management plan that incorporates assessment and treatment of both depression and pain is recommended²

1. Kroenke K *et al.* JAMA 2009; 301(20):2099-2110.

2. Bair MJ *et al.* Arch Intern Med 2003;163(20):2433-2445.

Mrs BB

- 66 yo
- L sided facial pain since June 2005 – TN diagnosed
- Tegretol - SE
- Epilim and Gabapentin - tremor, ataxia
 - Pain improved but ongoing constant pain and intermittent sharp stabbing pain 5-6 times per day
- Aware that distraction improves pain
- Lyrica - No improvement
- Trileptal – Rash
- Duloxetine
 - Marked (60%) improvement 7/10 – 3/10

CHRONIC PAIN MANAGEMENT

- Focusing on a single treatment modality may fail to address important aspects of the patient's pain experience¹
 - false beliefs and poor habits
 - unrealistic expectations
 - depression and anxiety
- A multimodal (team) approach is preferred,¹ involving:
 - non-pharmacological therapies
 - pharmacotherapy
 - referral to other healthcare professionals
 - procedural interventions

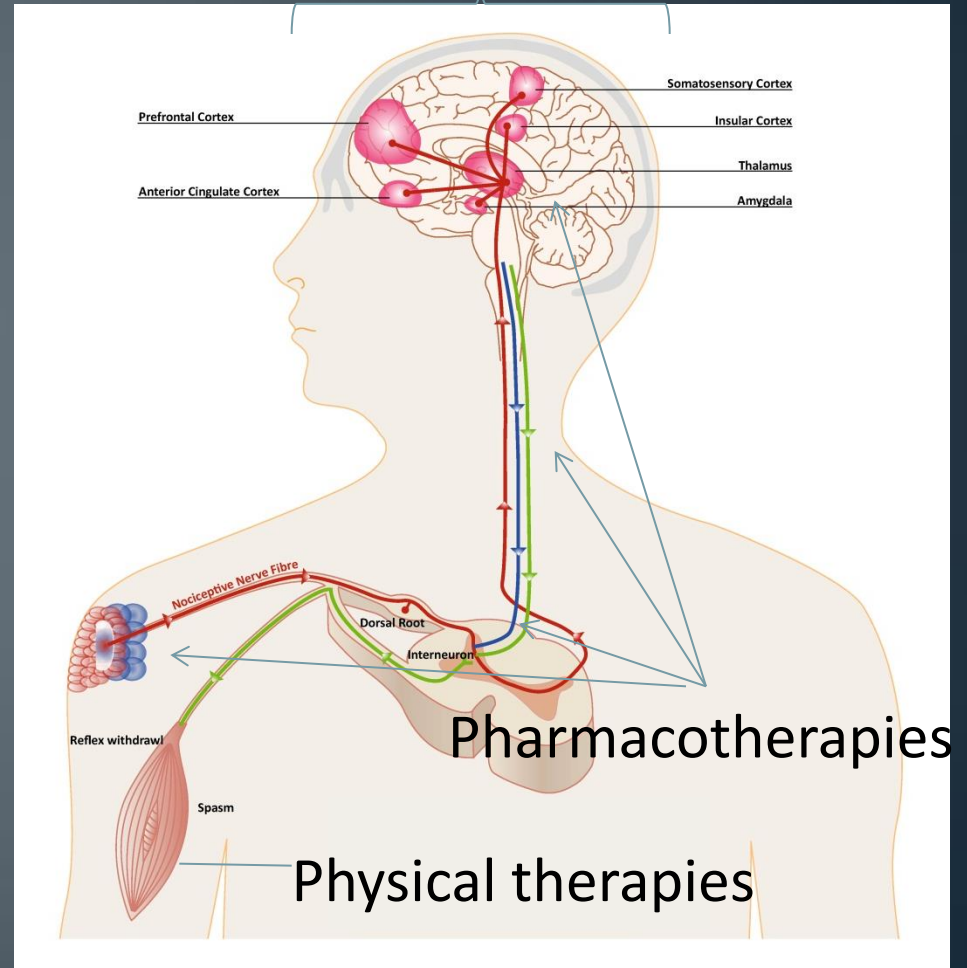
COGNITIVE APPROACH

- Pain is a perception, filtered through the brain
 - Stimulus is only perceived as pain because the brain interprets the stimulus as pain
- Brain is the organ that processes cognition and emotions
- Brain is responsible for integrating sensory, cognitive and emotional information as part of the interpretation process involved in pain perception

MULTIMODAL PAIN MANAGEMENT

- The focus of pain management is on improvement condition, function and activity
- Combining:
 - Physical therapies
 - Cognitive therapies
 - Pharmacotherapies

Psychological therapies



1. Cohen ML, Wodak AD. Medicine Today 2010;11:10-18.

2. Analgesic Expert Group. Therapeutic Guidelines: Analgesic. Version 5. 2007.

CUSTOMISING TREATMENT

The search for pain freedom

Right patient(s)

Right drug(s)

