TRIGEMINAL NEURALGIA MEDICATIONS NOT WORKING –

PRESENT TO ED or NOT??.

A/Professor Arun Aggarwal

Royal Prince Alfred Hospital
Pain Management Centre
SYDNEY AUSTRALIA

July 2022

AAN Summary of Evidence-based Guideline for CLINICIANS

TRIGEMINAL NEURALGIA

PHARMACOLOGICAL TREATMENT	
1. Which drugs effectively treat CTN pain?	
Strong evidence	Strong evidence supports that carbamazepine should be offered to treat CTN pain (**Level A**).
Good evidence	Good evidence supports that oxcarbazepine should be considered to treat CTN pain (**Level B**).
Clinical context	The two drugs to consider as first-line therapy in TN are CBZ (200-1200 mg/day) and OXC (600-1800 mg/day). Although the evidence for CBZ is stronger than for OXC, the latter may pose fewer safety concerns.
Weak evidence	Weak evidence supports that baclofen, lamotrigine, and pimozide may be considered to treat CTN pain (**Level C**).
Good evidence	Good evidence supports that topical ophthalmic anesthesia should not be considered to treat CTN pain (**Level B**).
Clinical context	There is little evidence to guide the clinician on the treatment of TN patients who fail first-line therapy. Some evidence supports add-on therapy with lamotrigine or a switch to baclofen (pimozide being no longer in use).

Australian Pain Society (APS) 2008 recommendations for the pharmacologic management of Neuropathic pain

APS-preferred medications available in Australia for treatment of neuropathic pain conditions*	
Noradrenergic antidepressants	Nortriptyline[a], amitriptyline[a], venlafaxine[a], duloxetine[a]
Calcium channel alpha 2-delta ligands	Gabapentin, pregabalin
Sodium channel blockers	Carbamezepine, topical lignocaine[a]
Opioid agonist	Morphine, oxycodone, methadone
Partial opioid agonist / monaminergic	Tramadol / (Tapentadol–Aggarwal 2017)

[a] * Non-prioritised

Nortriptyline, amitriptyline, venlafaxine, topical lignocaine are not indicated for the treatment of neuropathic pain in Australia; duloxetine is indicated for the treatment of diabetic peripheral neuropathic pain in Australia

The APS recognises that multiple drug regimens may increase the successful outcome rate, that the drugs may require rotation, and that effectiveness and side-effects must be continually monitored

NP, neuropathic pain

NEUROPATHIC PAIN THERAPIES AUSTRALIA 2022 *(AGGARWAL)*

- **Anti-Convulsants**
  - **Carbamazepine, Oxcarbazepine**
  - **Valproate, Phenytoin**
  - **Gabapentin, Pregabalin**
  - **Lamotrigine, Topiramate, Levetiracetam, Tiagabine**
  - **Lacosamide (Vimpat), Zonisamide, Fycompa (Perampanel – AMPA)**
  - **Clonazepam**
- **Anti-Depressants**
  - **Amitriptyline, Nortriptyline, Imipramine**
  - **Duloxetine**
- **Opioids**
  - **Tramadol, Buprenorphine, Oxycodone (Targin), Tapentadol, Morphine, Fentanyl, Hydromorphone**
- **Miscellanous**
  - **Baclofen, Mexilitene, Clonidine, Capsaicin cream**
- **N-methyl-D-aspartate (NMDA) blockers**
  - **Dextromethorphan, Physeptone, Ketamine, Memantine**
- **Versatis – Lignocaine 5% dermal patch**
- **Vitamin B12**
- **Botulinum Toxin**
- **Medicinal Cannabis**
  - **Tilray THC10:CBD 10 / Tilray CBD 100 / Nanabis THC:CBD / NanaCBD / Althea**

NNT'S FOR PERIPHERAL NEUROPATHIC PAIN STATES

Carbamazepine	2.3	(CI 1.6 - 3.8)
Sodium Valproate	2.3	
Amitriptyline	2.4	(CI 2.4 – 4.0)
Gabapentin	3.8	(CI 3.5 - 5.7)
Pregabalin	4.2	(CI 3.9 – 6.6)
Tramadol	3.9	(CI 2.7 - 6.3)
Lamotrigine	4.0	(CI 2.1 - 4.2)
Topiramate	7.4	(CI 4.3 – 28.5)

Tegretol CR

- **First-line agent**
  - 100mg nocte increasing slowly to 400mg bd – maximum 1200mg / day
- **Serum therapeutic ranges are irrelevant**

Oxcarbamazepine (Trileptal)

- Carbamazepine with less side effects
  - Less Na, dizziness, drowsiness and lethargy
- Slightly less potent than Tegretol
  - Higher doses may needed – **up to 1800 mg / day**
- 4 studies in Canada and Europe
  - As effective as Carbamazepine (70-80% response)
- Not covered by PBS
  - Approx $90 per month

Sodium Valproate

- Better tolerated than Carbamazepine
- Increases activity of the inhibitory transmitter GABA
  - t ½ 8-12 hrs
- Only 1 clinical trial in pain
  - 89 patients – NNT 2.3
- 200mg nocte increasing to 400mg bd **(max 2000 mg / day)**
- **Stillman MJ. Headache 2004**
  - 130 patients with headache - dose ranged from 300-1200mg
  - 57.5% responded to the first treatment
- SE: GIT, weight gain, tremor
  - Hepatic dysfunction
  - Monitor LFT's

Intravenous Valproate (Epilim)

- 10 mg / kg with 4ml NS slow infusion over 5 mins then continuous infusion of 1 mg/kg/hr for next 4-6 hours, according to clinical response
- **Schwartz TH. Headache 2002**
  - IV Valproate 15mg/kg followed by 5kg/kg every 8hr
  - Improvement in headache in 80%

Pregabalin (Lyrica)– On PBS

- **Works on alpha-2-delta ligand**
  - t ½ 2.5 hrs – reaches steady state within 24-48 hours
  - Analgesic, anxiolytic and anti-convulsant
- **SE's**
  - Dizziness, somnolence, blurred vision
  - Weight gain and peripheral oedema
- **Dosage**
  - 25mg nocte increasing slowly to 150mg bd **(max 600 mg bd)**
  - 25mg much better tolerated than 75mg as starting dose

Gabapentin (Not on PBS but affordable - $20/mth)

- **Used in a variety of neuropathic pain conditions**
  - Prevent allodynia and hyperalgesia
  - Improves pain and sleep
  - NNT better than Pregabalin 3.8 cf 4.2
  - **Effective even if tried and failed Pregabalin**
- **Designed as an analogue of GABA**
  - Acts also on NMDA receptors
  - t ½ 5-7 hrs – renal excretion
- **Dose**
  - 100mg nocte titrating up to **1800mg/day**
  - 100mg better tolerated than 300mg as starting dose
- **SE's**
  - Drowsiness, dizziness, ataxia

Intravenous Phenytoin

- Blocks sodium channels
  - Inhibits pre-synaptic glutamate release
- **McCleane GJ. Anesth Analg 1999**
  - Randomised, D-B, P-C study of 20 patients with acute flare-ups of neuropathic pain
  - 2h placebo infusion cf 15mg/kg Phenytoin (av. 1000mg)
  - Slow infusion – given over 1 hour
  - Reduced burning, shooting pain and sensitivity for 4 days
  - Alkaline pH – burning pain and IV site irritation

Intravenous Keppra

- IV infusion
  - 1000 mg over 15 min
  - Dizziness, somnolence, fatigue, headache

Intravenous LACOSAMIDE (VIMPAT)

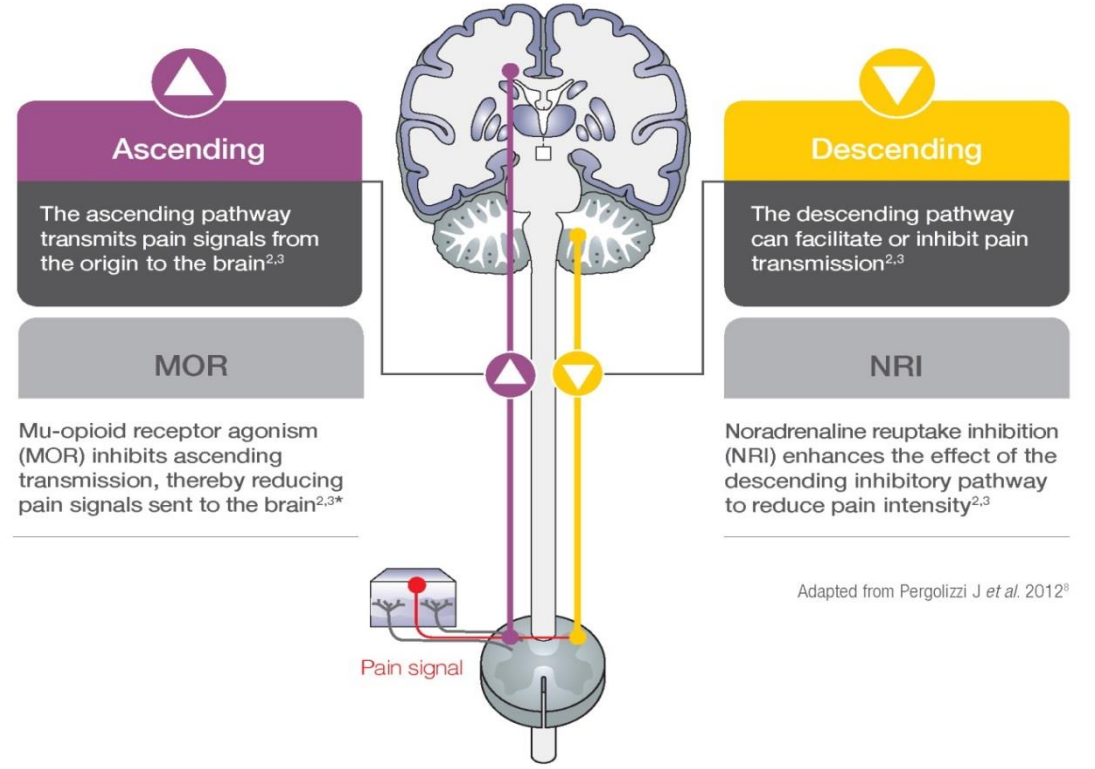
- Selectively enhances slow inactivation of voltage-gated sodium channels
  - Reduced hyper-excitabilitity of membranes
- Loading dose 200mg infused over 60 minutes. - Repeat after 12 hours if required

Opioids Place in Persistent Pain

- **Beneficial in some patients**
  - Demonstrated good efficacy outcomes
  - Only moderate side effects
  - Low risk of abuse or addiction
- **Longer acting opioids are better than short-acting**
- **Patient selection and close follow-up important – Multi-modal approach**
- **Efficacy of acute (IV) to opioids in TN**
  - Effective but dose dependent response
  - Pain intensity reduced by 13 points compared to placebo
    - ie 20-30% reduction
- **Consider TAPENTADOL** – atypical opioid

TAPENTADOL (PALEXIA®) SR / IR: Mechanism of Action†

(complementary and interact synergistically)



†Animal data do not necessarily predict human clinical effect

*mu-opioid receptor agonists also activate the inhibitory descending pain pathway at a supraspinal level, however their efficacy in chronic neuropathic pain may be limited and require higher doses than for nociceptive pain[4-6]

Refs: 1. Pergolizzi et al. Pain Prac 2011; 12(4):290–306. 2. Argoff C. Curr Med Res Opin 2011; 27(10):2019–31. 3. Kress HG. Eur J Pain 2010; 14(8):781–3. 4. eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; Mar 2013 Accessed: 5 May 2014. 5. Ballantyne JC & Shin NS et al. Clin J Pain 2008; 24(6):469–78. 6. McNicol ED et al. Cochrane Database Syst Rev 2013; (Issue 8). 7. Schroder W. Et al. Eur. J. Pain 2010; 14:814-821

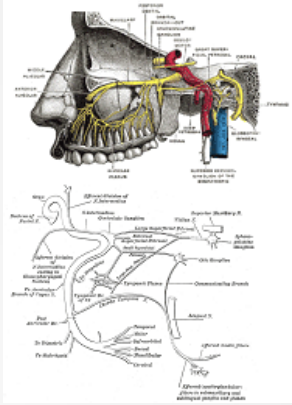
Vitamin B12

- **Used by the body in the production of myelin**
- **Gross deficiencies**
  - Lead to nerve damage (pain and inflammation)
  - Beef, lamb, eggs, liver, oysters
- **Parenteral B12 or oral 1000 mcg daily**
  - Hydroxocobalamin / cyanocobalamin / Methylcobalamin
- **Help regenerate myelin and nerve cells, even in non-deficient**
- **Initial studies (1940's) -promising results**
- **Talaei 2009**
  - Parenteral vitamin B(12) vs nortriptyline in DPN – 100 patients
    - Pain decreased 3.6 on NRS with vitamin B12 and 0.8 Nortriptyline

CROMWELL PROPERTY GROUP Foundation

- **TN / facial pain is NOT an approved indication for the use of Botox, so the cost of toxin needs to be covered for PRIVATELY**
- Minimum cost is 1 x 100U vial of Botox approx. **$600** with no reimbursement through PBS (even for pensioners)
- Some private health funds may reimburse, but generally still consider "cosmetic"
- **In 2016, the CROMWELL Foundation** provided a research grant to study Botox in TN and these are the results:

Spheno-palantine Ganglion



- The SPG is the largest group of nerves outside the brain and is located in the sphenopalatine (pterygopalatine) fossa at the back of the nose
- It receives sensory connections from V2 with some autonomic connections to the facial Nerve (VII)
  - Upper cervical (C_2, C_3, C_4,) roots have some indirect connection with trigeminal system via maxillary nerve
    - Cause "referred" pain to head and facial, and vice versa
- SPG block can be very effective in facial pain and headache

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 for Dextromethorphan**
    - As a cough suppressant 40-80mg
    - Pain 400mg / day

  - **Dextromethorphan NNT for DPN** **2.5 (CI 1.6 - 5.4)**
  - **Dextromethorphan NNH** **8.8 (CI 5.6 – 21.1)**

AV. DAILY KETAMINE DOSE

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

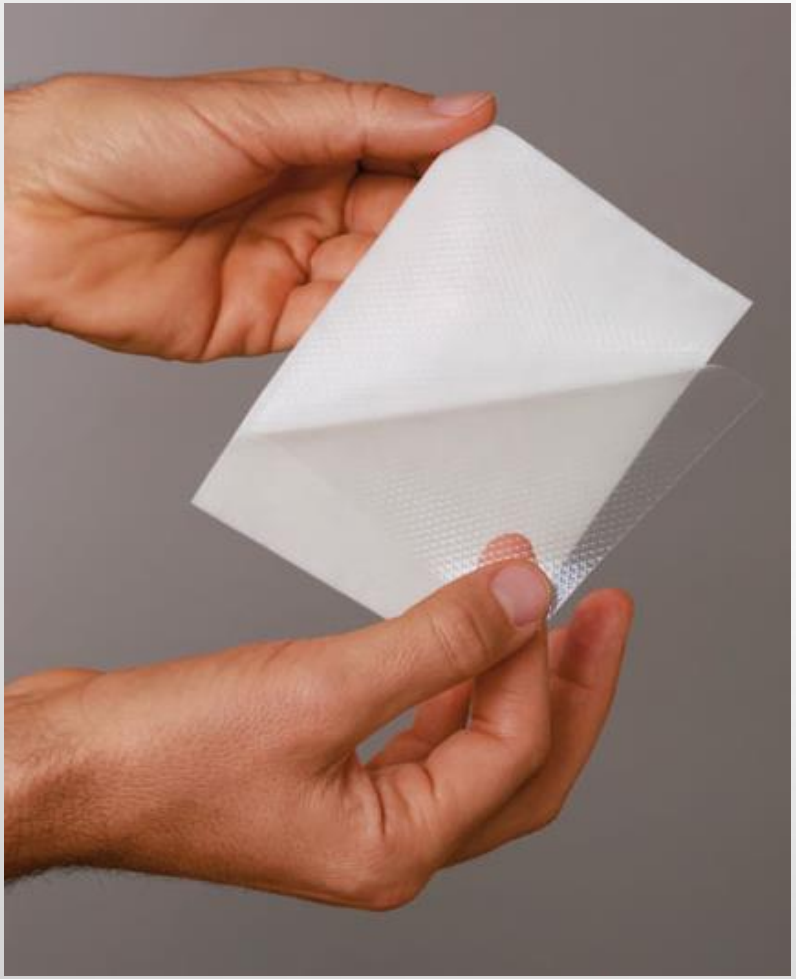
50ml Syringe
Ketamine 200 mg +/- Lignocaine 2000 mg (2x10ml x10% xylocaine) sub-cutaneously

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**

Intravenous Lignocaine

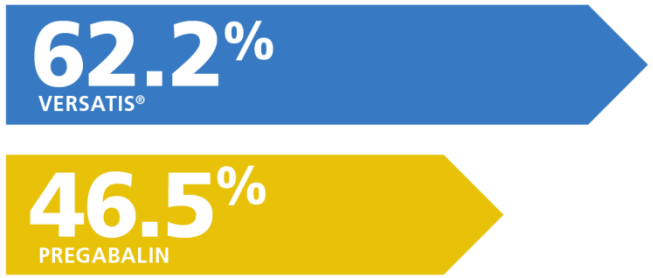
- Sodium channel blocker
  - Reduces spontaneous and evoked responses in a variety of neuropathic pain conditions
- 2000mg (2 x 10 ml x 10% xylocaine – lignocaine HCl)
  - 40mg/ml
  - 1mg/kg/hr
  - Monitor BP and HR
- Relief within 20 minutes after end of infusion and persisted for over 10 hours

Topical approach for the management of Neuropathic Pain - Versatis



- Pharmaceutical formulation[1]: 5% lignocaine w/w plus hydrogel-patch
- Size: 10 cm x 14 cm[1]
- Absorption: 3% ± 2% of the lignocaine dose systemically absorbed[1]
- Administration: 12 hours on and 12 hours off[1]
- Indication: Symptomatic relief of neuropathic pain

Responder rate*, after 4 weeks of treatment (n=88)[1†‡]



1 Versatis® Product Information July 2015.
2 Baron, Pain Ther 2016

Medicinal Cannabis - $120 / month

- Medicinal cannabis products are unapproved drugs but now may be accessed by certain medical practitioners
- The active compounds found in the cannabis plant are referred to as cannabinoids
  - Cannabidiol (CBD), the major non-psychotropic compound
  - Tetrahydrocannabinol (THC) the compound that gives cannabis its psychotropic effect
- ***Medical Cannabis Treatment in Patients with Trigeminal Neuralgia – 2019***
  - 42 patients (32=female 10=male)
  - 81% reported improvement in their TN symptoms
    - Of patients who reported ≥50% improvement in TN symptoms, 69% used one product and 50% used a 1:1 ratio of THC:CBD.
    - 50% were able to reduce their opioid consumption
  - AE were reported in 40%

Efficacy of Erenumab in the Treatment of Trigeminal Neuralgia: A Retrospective Case Series

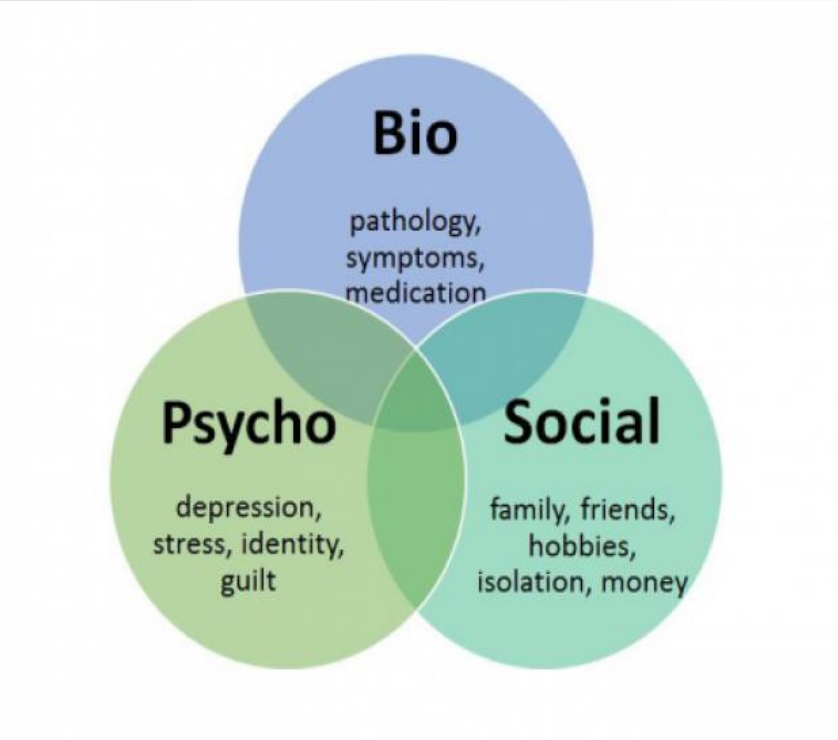
Eliot Parascandolo [1], Kelsey Levinson [1], Paul Rizzoli [1], Roni Sharon

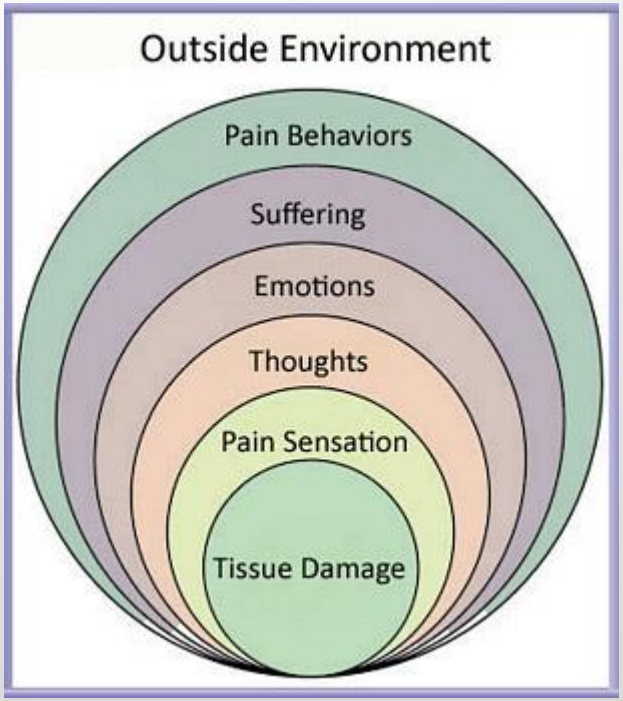
- **Objective:** CGRP plays a role in both TN and migraine.
  - Erenumab, a human anti-CGRP monoclonal antibody medication, modulates CGRP, which is elevated in patients with TN.
- **Methods:** 10 patients diagnosed with TN and treated with erenumab for 6 months. Pain was tracked using a numeric pain rating scale (NPRS) from 0 to 10. The effect of erenumab on NPRS after 6 months' time was the primary end point.
- **Results:** 9 of 10 patients (90.0%) reported improvement in pain severity and in global mood improvement.
  - 3 patients reported resolution of anxiety and/or depression.
  - Side effects were minimal, with 3 patients reporting constipation, injection site reactions, or both.

Conclusions: Erenumab appears to be an efficacious treatment option for patients with refractory TN.

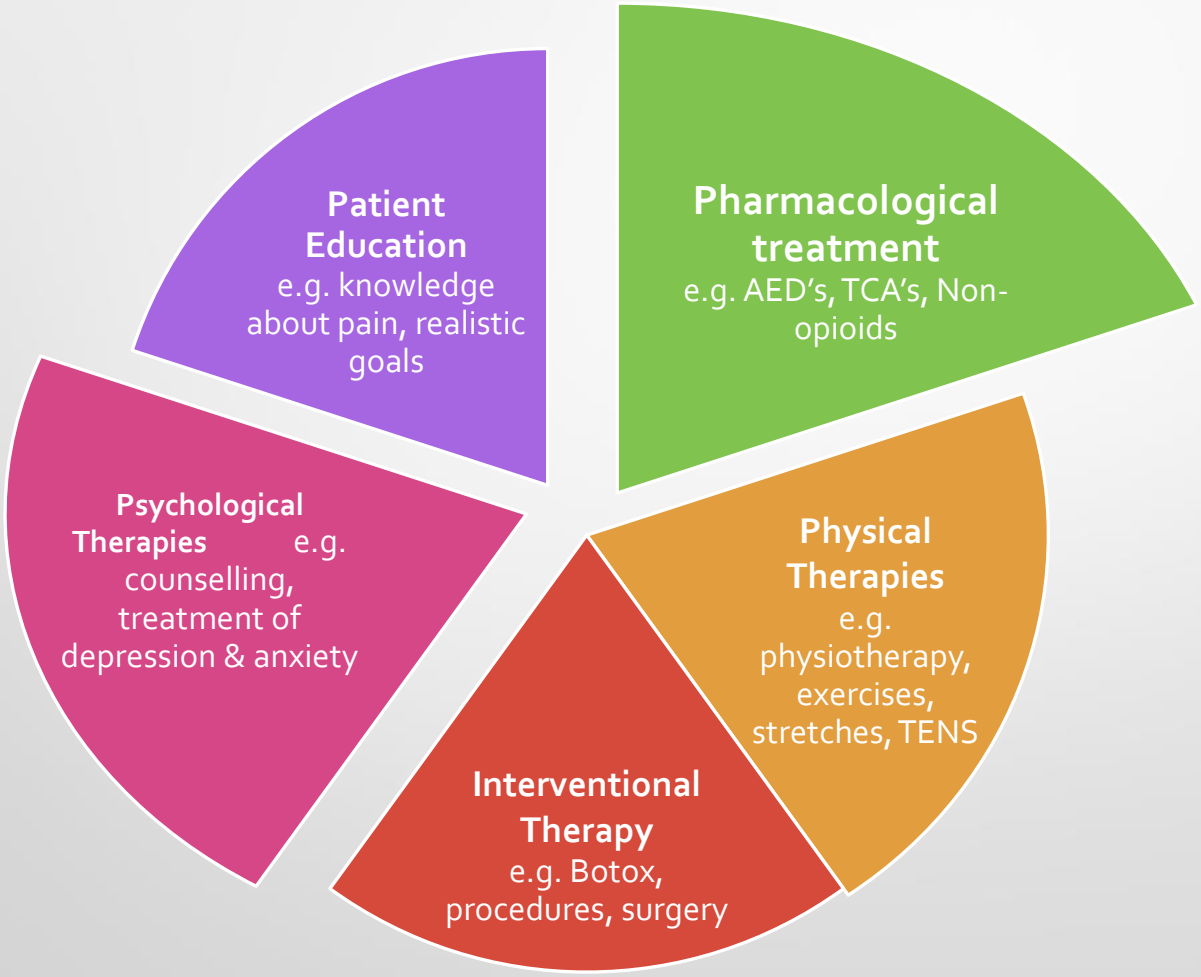
MANAGING PERSISTENT PAIN

- **Effective pain management requires comprehensive assessment which incorporates:**
  - **Biological** – nociceptive or neuropathic
  - **Psychological** – anxiety, depression, negative thoughts
  - **Social factors** - litigation, cultural, financial, isolation





THE MULTIMODAL APPROACH TO CHRONIC PAIN MANAGEMENT



1. Pergolizzi J. Curr Med Res Opin 2013;29(9):1127-1135.

THE UNIVERSITY OF SYDNEY

A/Prof. Arun Aggarwal

Ph.D., F.R.A.C.P., F.A.F.R.M.(R.A.C.P), F.F.P.M.(A.N.Z.C.A.)

Clinical Associate Professor

of Neurology, Neurophysiology, Rehabilitation / Pain Medicine

AGNI Health Centre
190 Victoria Road
(cnr. Moodie Street)
Rozelle, NSW. 2039
Ph: 02 9810 6633

6/49 Palmerston Road
(opp. Hornsby Hosp.)
Hornsby, NSW. 2077
Ph: 02 9477 2780

ROYAL PRINCE ALFRED, BALMAIN and CONCORD PUBLIC HOSPITALS
HUNTERS HILL, METROPOLITAN and STRATHFIELD PRIVATE HOSPITALS

E-mail: arun.a@sydney.edu.au Fax: 02 9817 6633