

Management of Neuropathic Pain



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Neuropathic Pain



- “Pain initiated or caused by a damage, disease or dysfunction in the nervous system, in the absence of an ongoing peripheral noxious stimulus”
- Comprises about 25 - 40% of chronic pain referrals
- Generally responds poorly to conventional analgesics

Neuropathic pain features

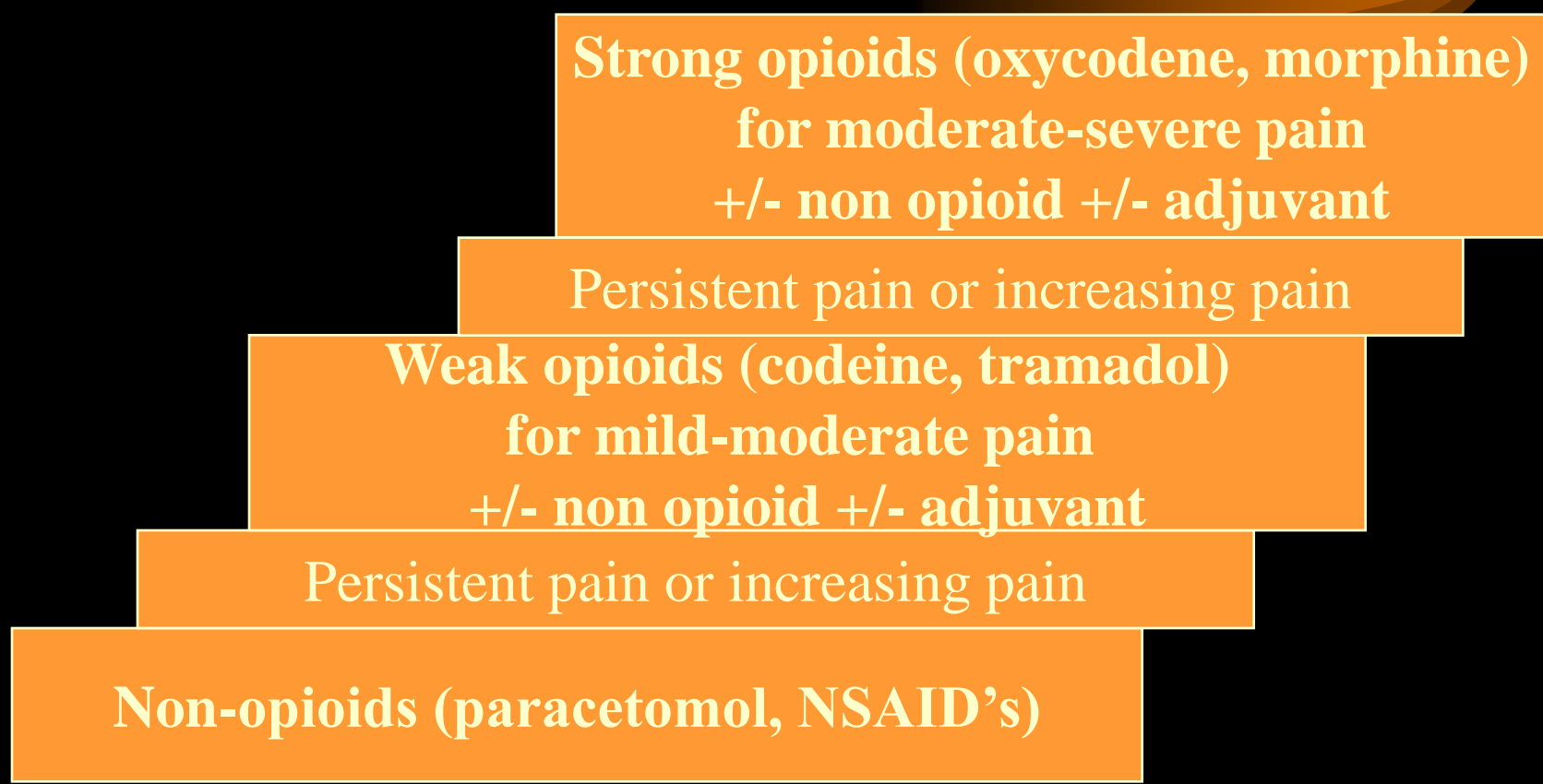
- Pain delayed months or even years after original injury
- Absence of ongoing peripheral tissue damage
- Sharp, shooting, stabbing, knike-like, electric-shock like, lacinating, burning and pins and needles
- Spontaneous or stimulus evoked pain
- **Dysaesthesias**
- **Allodynia**
 - Pain to a non-painful stimulus
- **Hyperalgesia**
 - Increased pain to a painful stimulus

Treatment Principles

- Multi-modal treatment approach
- Realistic expectations
 - Complete relief of pain is unlikely
 - Adequate education for realistic goals
 - Unmet expectations lead to frustration, hopelessness and anger
- Regular medication not PRN
 - Reducing need for patients to monitor pain levels

WHO Analgesic Ladder

(generally for nociceptive pain)



The diagram illustrates the WHO Analgesic Ladder as a series of four ascending steps, each represented by an orange rectangular box. The steps are arranged from bottom-left to top-right, indicating a progression of treatment. A horizontal decorative bar with a purple-to-yellow gradient is positioned above the top two steps. The text within each box is white and bold.

**Strong opioids (oxycodone, morphine)
for moderate-severe pain
+/- non opioid +/- adjuvant**

Persistent pain or increasing pain

**Weak opioids (codeine, tramadol)
for mild-moderate pain
+/- non opioid +/- adjuvant**

Persistent pain or increasing pain

Non-opioids (paracetamol, NSAID's)

Number needed to treat

	Success	Fail	Rate
Treatment	40	10	0.8
Control	30	20	0.6

- Attributable effect = $0.8 - 0.6 = 0.2$
- $\text{NNT} = 1/0.2 = 5$ i.e. treat 5 patient to get 1 positive response due to the treatment.
- $\text{NNT} < 3$ is good

Treatment??



Tricyclic Anti-depressants



- Commonest first line adjuvant used for over 40 years for neuropathic pain
- Inhibition of serotonin and noradrenaline reuptake
- Enhance endogenous inhibiting descending pain pathways from brainstem to spinal dorsal horn

Tricyclic Anti-depressants

- TCAs are adjuvant analgesics:
 - Effective analgesic dose lower (5-25mg) than primary indication (100-150mg)
 - Onset of action for adjuvant benefits (analgesic effects) generally occur faster within 3-4 days rather than 2-3 weeks for depressive symptoms
 - Direct analgesic effect & relieve other common symptoms such as sleep disorder

Tricyclic Anti-depressants



- Amitriptyline
- Nortriptyline
- Doxepin
- Adverse side effects:
 - anticholinergic effects
 - sedation, dry mouth, blurred vision, urinary retention
 - life-threatening cardiovascular effects (arrhythmia)

Tricyclic Anti-depressants

- McQuay - meta analytic review of 21 randomised control trials
 - Diabetic neuropathies - 6 out of 13 reports using 9 different antidepressants showed benefit of all compared with placebo
- NNT was 2.9 (2.4 - 4), with a NNH was 3.7 (2.9-5.2) and withdrawal was 22

SSRI Anti-depressants



- Selective serotonin reuptake inhibitors
 - Sertraline (Zoloft), fluoxetine (Prozac) and paroxetine (Aropax)
 - Paroxetine reduced pain in neuropathy, but 40 mg was not superior to placebo
- Non-TCA, non-SSRI antidepressants
 - Venlafaxine (Efexor) and nefazodone (Serzone)

SNRI Anti-depressants



- **Duloxetine**
 - Selective serotonin and NAR reuptake inhibitor
 - 30 mg mane increasing to 60 mg mane
- Diabetic PN
 - 50% reduction in pain in 50% of patients in week
- SE's
 - Nausea, dry mouth, constipation, insomnia

Anti-convulsant drugs



- Used since the 1960's esp lacinating or burning
- **Carbamazepine (Tegretol CR)** was first-line agent
- Important side effects include:
 - cognitive, hyponatremia
 - bone marrow suppression, skin rashes
 - liver function abnormalities
- Serum therapeutic ranges are irrelevant

Anti-convulsant drugs



- **Epilim**
 - Better tolerated
 - Increases activity of the inhibitory GABA
 - Hepatic dysfunction should be monitored
- **Clonazepam**
 - Benzodiazepine, but low dose
 - Facilitates binding of GABA to its receptors
 - Esp. burning feet due to restless legs

Anti-convulsant drugs



- **Gabapentin**
 - Designed as an analogue of GABA
 - Used in a variety of neuropathic pain conditions
 - Prevents allodynia and hyperalgesia
 - Acts also on NMDA receptors
- Improves pain and sleep
 - Dose - 300mg nocte titrating up to 1800mg/day
 - SE's - drowsiness, dizziness, ataxia

Amitriptyline vs Gabapentin



- Morello 1999
 - No difference between Gabapentin 900 – 1800 mg / day and Amitriptyline 25-75mg /day in double blind study of 25 patients
- Dollacchio 2000
 - Not blinded, but still showed no significant difference
 - Gabapentin 400-2400 mg /day (8/13) and Amitriptyline 10-90mg /day (7/12)
 - Both >50% reduction in pain scores

Anti-convulsant drugs

- **Pregabalin**

- TGA approved for neuropathic pain BUT not reimbursable
- Works on alpha-2-delta ligand
- Analgesic, anxiolytic and anti-convulsant
- SE: somnolence, dizziness, dry mouth

- Siddall PJ. 2005

- 137 patients chronic central neuropathic pain
- 42% improved pain by >30% and improved sleep
- Improvement within 1 week

Pregabalin

- Pooled data from 6 double-blind, placebo-controlled, multi-centre studies in diabetic PN -bd and tds dosage
- Patient global impression of change (PGIC) scale
 - Global measure of effectiveness that indicates how patients might or might not be benefiting from treatment
- LYRICA 300 and 600 mg/day
 - Significant improvement in overall compared to placebo - dose related
 - 70% on LYRICA 300 mg/day and 80% on 600 mg/day reported significant improvement in their overall status BUT
 - 55% of placebo group also improved – NNT between 4-5

Pregabalin

	<i>Placebo (n=764)</i>				<i>All Pregabalin doses</i>	
		<i>150 (n=427)</i>	<i>300 (n=509)</i>	<i>600 (n=459)</i>	<i>Incidence (n=1556)</i>	<i>Discontinued (n=1556)</i>
<i>Dizziness</i>	<i>6.4</i>	<i>13.3</i>	<i>25.5</i>	<i>29.6</i>	<i>21.7</i>	<i>3.1</i>
<i>Somnolence</i>	<i>3.8</i>	<i>9.8</i>	<i>15.9</i>	<i>17.6</i>	<i>13.8</i>	<i>2.6</i>
<i>Peripheral oedema</i>	<i>1.8</i>	<i>5.2</i>	<i>12.0</i>	<i>13.5</i>	<i>9.5</i>	<i>0.8</i>
<i>Dry mouth</i>	<i>1.8</i>	<i>4.7</i>	<i>5.3</i>	<i>8.1</i>	<i>5.9</i>	<i>0.3</i>

Anti-convulsant drugs



- All AEDs have potential for adverse cognitive and behavioral side effects.
 - sedation, confusion
 - diplopia, vertigo, and ataxia
- Overall NNT for effectiveness is about 2.5, NNH was 3 and withdrawal 20
- Some patients benefit from both AED and TCA

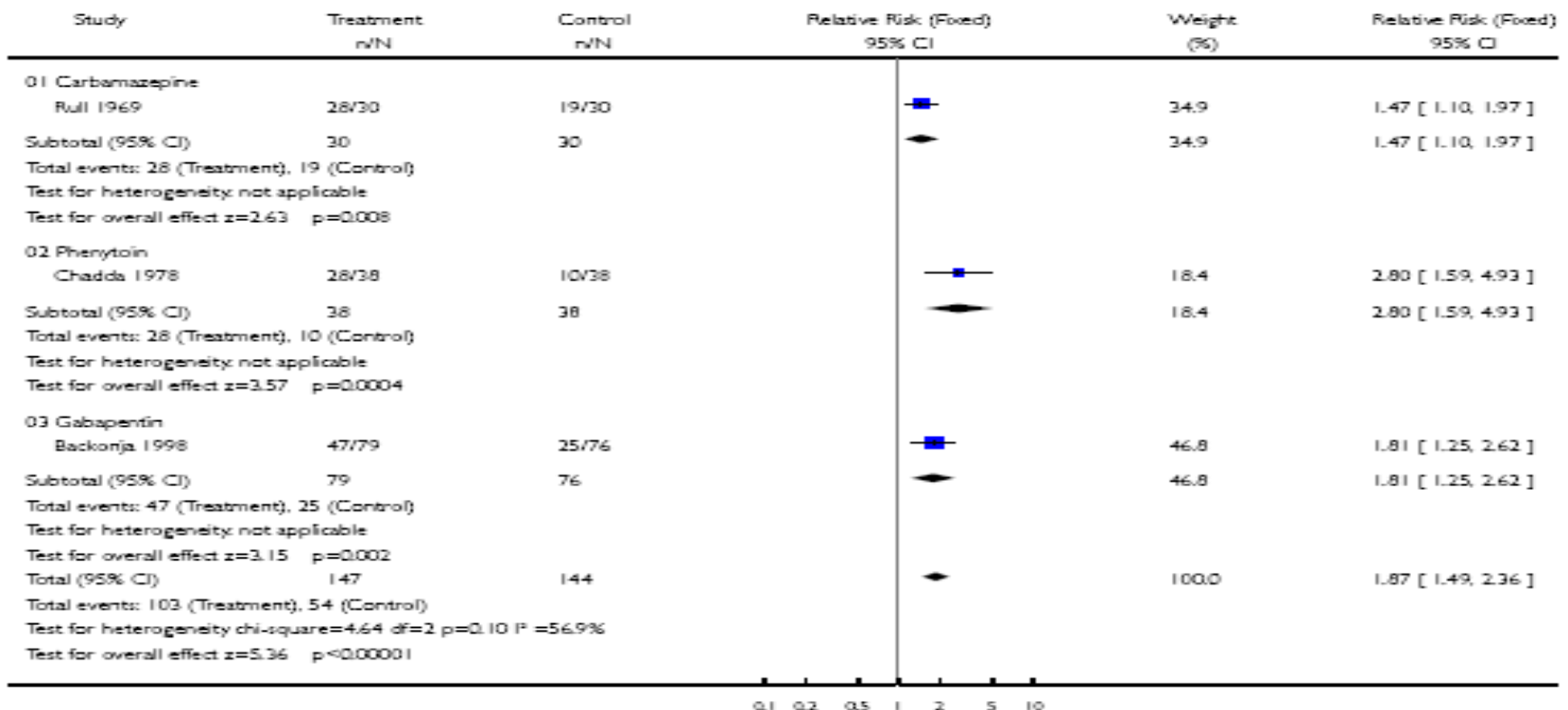
Anti-convulsant drugs

Analysis 01.02. Comparison 01 Neuropathic Pain, Outcome 02 Diabetic neuropathy

Review: Anticonvulsant drugs for acute and chronic pain

Comparison: 01 Neuropathic Pain

Outcome: 02 Diabetic neuropathy



NNT for Diabetic PN

- Tegretol 2.3 (CI 1.6-3.8)
- Amitriptyline 2.9 (CI 2.4 - 4)
- Gabapentin 3.8 (CI 3.5-5.7)
- Pregabalin 4 - 5
- Tramadol 3.8 (CI 2.8 to 6.3)

Cochrane report states that whilst Gabapentin and Pregabalin are gaining popularity as a treatment for neuropathic pain, no clear advantage has been demonstrated over Tegretol

NNH for Diabetic PN

- 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
 - Opioids 4.2 (CI 3.2-5.6)
 - Tramadol 8.3 (CI 5.6-17) quick and slow

Opioids

- Lack of definitive evidence regarding efficacy in reducing neuropathic pain therefore discourage use of opioids in the treatment of neuropathic pain
- Concerns about adverse effect profiles and potential for abuse and addiction
- 2 trials in neuropathic pain
 - Gilron 2005 - non-significant superiority of morphine to gabapentin
 - Raja 2002 - non-significant superiority of morphine and methadone to nortriptyline - 4.4 vs 5.1 - low numbers 120

Tramadol



- CNS-active analgesic, synergistic action via:
 - Reuptake inhibition of serotonin and noradrenaline and weak binding to mu-opioid receptors
 - Quick –acting - 50 mg twice a day to four times a day, SR and XR
- 100 - 400 mg effective treatment for peripheral neuropathic pain
- NNT compared to placebo 3.8 (CI 2.8 to 6.3)
- NNH was 8.3 (CI 5.6 to 17)
- Side effects: CNS (sedation, confusion, dizziness), gastrointestinal (nausea, constipation, dry mouth) and risk of seizures

Miscellaneous Agents

- **Mexilitine**

- Blocks sodium channels
- Reducing abnormal baseline and inducible nerve discharges
- Difficult to initiate and poorly tolerated

- **Baclofen**

- Strong GABA b receptor agonist
- Initiate slow 5 mg orally, may be increased to 40-60 mg/day
- Side effects: CNS depression - sedation, confusion, dizziness, nausea and postural hypotension

NMDA receptor antagonists



NMDA receptor antagonists



- **Ketamine**
 - Non-competitive NMDA antagonist
 - Use limited by due side effects (hallucinations)
 - Developed in 1963 to find a safer alternative to PCP
- Anaesthetic with:
 - Dissociative (separates perception from sensation),
 - Analgesic, sedative and amnesic properties
- Used in veterinary medicine
- Odorless, tasteless, undetectable in drinks

Ketamine

- **Ketamine infusion** – 200mg in 50ml at 0.1mg/kg/hr run at 2ml/hr
- **Oral Ketamine** - 20mg bd
- **Topical Ketamine gel** - 0.093 mg/kg – 9.33 mg/kg
- **Ketamine lozenges** – 25mg bd initially
- **Harbut RE. Pain Med 2004**
 - Low dose ketamine infusion
 - 33 patients 1996-2002 with CRPS
 - Pain completely relieved in 25 of 33 patients
 - 54% remained pain free for 3 months or more
 - 31% for 6 months or more

Anaesthetic blocks



- **L2 paravertebral blocks**
 - Innervation of disc with nerve root distribution of pain
 - Pain on flexion and sitting
- **Peri-radicular blocks**
 - Nerve root compression with radicular symptoms
- **Epidural blocks**
 - Disc pain with radicular pattern
- **Facet joint blocks**
 - Pain on extension
 - Pain usually not below knee

Pain Clinics



- Multi-disciplinary
- Medication
 - Analgesic, anti-neuropathic and psychotropics
- Nerve blocks
- TENS
- Physical interventions
- Psychological interventions

Chronic Pain Concepts



- Hurt does not equal harm
- Reduce fear avoidance behaviours
- Take an “active role” in management
- Avoid pain behaviour
- Pacing
- Communication and education
- Cognitive and behavioural modification

Spinal cord stimulation

