Pharmacotherapy for Pain Disorders

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Dr John Alchin, FFPMANZCA
Pain Medicine Specialist
Pain Management Centre, Burwood Hospital,
Christchurch, NZ

Definition of pain
(IASP, 1979)

“Pain is an unpleasant sensory & emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

NB: “Unpleasant” hardly captures the extreme suffering of some chronic pain
**Figure 8 (page 1836): Leading causes of age-standardised YLD rates globally, 2017**

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LBP</td>
<td>LBP</td>
</tr>
<tr>
<td>2. Headache</td>
<td>Headache</td>
</tr>
<tr>
<td>3. Depression</td>
<td>Diabetes</td>
</tr>
<tr>
<td>4. Fe Deficiency</td>
<td>Age-related Hearing Loss</td>
</tr>
<tr>
<td>5. Diabetes</td>
<td>Depression</td>
</tr>
<tr>
<td>6. COPD</td>
<td>Neonatal Disorders</td>
</tr>
<tr>
<td>7. Age-related Hearing Loss</td>
<td>Drug Use Disorders</td>
</tr>
<tr>
<td>8. Anxiety</td>
<td>Visual Loss</td>
</tr>
<tr>
<td>9. Neck Pain</td>
<td>COPD</td>
</tr>
<tr>
<td>10. Blindness</td>
<td>Other Musculoskeletal</td>
</tr>
<tr>
<td>11. Other Musculoskeletal</td>
<td>Neck Pain</td>
</tr>
</tbody>
</table>
Mechanistic Pain Descriptors 1 (IASP)

Nociceptive Pain

Pain due to threatened, or actual, tissue damage, causing activation of normally functioning nociceptors.

• This is the nociceptive system functioning as intended.

There are 2 types:

• **High intensity stimulus** in the absence of inflammation, eg a foot put in an unexpectedly very hot bath – **protective** function

• **Low intensity stimulus** in the presence of inflammation, eg sunburn – **healing** function
**Mechanistic Pain Descriptors 2**

**Neuropathic Pain**

Pain caused by a lesion or disease of the somatosensory nervous system.

- **Central**
  - SCI pain;
  - MS related pain;
  - Post-stroke pain

- **Peripheral**
  - Radiculopathy / radicular pain, entrapment neuropathies
  - Post-herpetic neuralgia
  - Painful diabetic peripheral neuropathy
  - Chronic post-surgical neuropathic pain

**Mechanistic Pain Descriptors 3**

**Nociplastic Pain**

(= “nociceptive plasticity,” i.e. pathological change in function of nociceptive pathways).

Pain characterized by clinical & psychophysical findings suggesting altered nociception, with:

- No evidence of actual or threatened tissue damage causing the activation of normally functioning nociceptors; and
- No evidence for disease or lesion of the somatosensory system.

*Term introduced by IASP in December 2017*
Mechanistic Pain Descriptors

• In nociceptive pain, the alarm is functioning as it should, warning the organism of problems, or potential problems, in the periphery.

• In contrast, neuropathic & nociplastic pain are “alarm” system problems, not problems with the peripheral tissues where the pain is felt. They are a “false alarm”.

*Pain Management Centres deal with alarm problems*
A nail gun backfired on builder Patrick Lawler, 23, on 6.1.05 while working in Breckenridge, a ski resort town in Colorado. The tool sent a nail into a piece of wood nearby, but Lawler didn’t realize a second nail had shot through his mouth. After the accident, Lawler had what he thought was a minor toothache and blurry vision. 6 days later, after painkillers and ice didn’t ease the pain, he went to a dental office.
“A builder aged 29 came to the accident and emergency department having jumped down on to a 15 cm nail. As the smallest movement of the nail was painful he was sedated with fentanyl and midazolam. The nail was then pulled out from below. When his boot was removed a miraculous cure appeared to have taken place. Despite entering proximal to the steel toecap the nail had penetrated between the toes: the foot was entirely uninjured.” Fisher JP et al. BMJ 1995;310:70

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**International Classification of Diseases version 11 (ICD-11)**


**MG30 Chronic pain**

persists or recurs for longer than 3 months.

**MG30.0 Chronic primary pain**

- chronic pain in one or more anatomical regions, characterized by:
- significant emotional distress (anxiety, anger/frustration or depressed mood); or
- functional disability (interference in ADLs & social roles).
- Chronic primary pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome.
International Classification of Diseases version 11 (ICD-11)

MG30.0 Chronic primary pain

- MG30.00 – chronic primary visceral pain
- MG30.01 – chronic widespread pain
- MG30.02 – chronic primary musculoskeletal pain
- MG30.03 – chronic primary headache/orofacial pain

International Classification of Diseases version 11 (ICD-11)

- MG30.1 Chronic cancer related pain
- MG30.2 Chronic post-surgical or post-traumatic pain
- MG30.3 Chronic secondary musculoskeletal pain
- MG30.4 Chronic secondary visceral pain
- MG30.5 Chronic neuropathic pain
- MG30.6 Chronic secondary headache or orofacial pain
### International Classification of Diseases version 11 (ICD-11)

- **MG30.1** Chronic cancer related pain
- **MG30.2** Chronic post-surgical or post-traumatic pain
- **MG30.3** Chronic secondary musculoskeletal pain
- **MG30.4** Chronic secondary visceral pain
- **MG30.5** Chronic neuropathic pain
- **MG30.6** Chronic secondary headache or orofacial pain

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**Chronic widespread musculoskeletal pain** could be either:
- **MG30.3**: Chronic secondary musculoskeletal pain – nociceptive pain, eg RA; or
- **MG30.01**: Chronic widespread pain – nociplastic pain, eg **fibromyalgia**

**Chronic musculoskeletal low back pain** could be either:
- **MG30.3**: Chronic secondary musculoskeletal pain – nociceptive pain, eg Ank Spon, or pathological #; or
- **MG30.02**: Chronic primary musculoskeletal pain – **nociplastic low back pain**

**Chronic large bowel visceral pain** may be due to:
- **MG30.4**: Chronic secondary visceral pain – nociceptive pain, eg Ulcerative Colitis; or
- **MG30.00**: Chronic primary visceral pain – nociplastic pain, eg **irritable bowel syndrome**
Pharmacotherapy

Moore A, Derry S, Eccleston C, Kalso E: “Expect Analgesic Failure; Pursue Analgesic Success”. *British Medical Journal*; BMJ 2013;346:f2690 (Published on-line 3 May 2013; print edition 08.06.13) – Doi: [http://dx.doi.org/10.1136/bmj.f2690](http://dx.doi.org/10.1136/bmj.f2690)

See also R. Andrew Moore:

### Evidence for analgesic efficacy in 4 types of pain

(“success” = 50% or more pain reduction in 50% or more of those randomised to active drug)

- **Acute postoperative pain** – only 4 of 10 analgesics.
- **Acute migraine** – only 1 of 6 medications
- **Chronic musculoskeletal pain** (osteoarthritis, chronic low back pain, fibromyalgia, ankylosing spondylitis) – none of 19 medications
- **Neuropathic pain** (painful diabetic neuropathy, post-herpetic neuralgia) – none of 9 medications

### Analgesia not normally distributed

“Pain relief is not normally distributed, but usually bimodal, being either very good (> 50%) or poor (< 15%).”

That is, any given analgesic tends to either:

- Work quite well (but only in a small minority of patients – 10-15%);
- Not work at all (in 85-90% of patients).
Fig. 1 Individual changes in pain over 14 weeks of treatment with pregabalin 450 mg in 200 patients with fibromyalgia

Responders vs Non-Responders

**Responders (a minority)**

- “success is often achieved within the first 2 weeks or so of treatment or not at all, & ... tends to last.”

- “Those who get better (responders) do well: . . . people who respond experience improvements in **fatigue**, **depression**, and **sleep** ... & general measures of **function** and **quality of life**, including **ability to work**.”

**Non-responders (the majority)**

“have none of these benefits.”
Minimise Side-Effects

An important advantage of this “responder analysis” approach to assessing analgesic efficacy is that it minimises patient exposure to adverse drug effects:

- In the (likely) event of analgesic trial failure, “patients without benefit should be exposed to no risk, because the drug is stopped; only effective drugs should continue to be prescribed.”

- On the other hand, “With success, considerable benefits in terms of pain relief, sleep, fatigue, depression, function, and quality of life, are balanced against rare risk of serious harm.”

NP – Strong Recommendations – 1st-Line

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/day)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic ADs</td>
<td>25-150</td>
<td>3.6</td>
</tr>
<tr>
<td>Nortriptyline (fewer side-effects than amitriptyline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200-3600</td>
<td>7.2</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300-600</td>
<td>7.7</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120</td>
<td>6.4 (not funded)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150-225</td>
<td>6.4</td>
</tr>
</tbody>
</table>

i.e., 1st-line pharmacotherapy for NP:

- Nor-adrenergic anti-depressants:
  - TCAs,
  - SNRIs
- Gabapentinoid anti-convulsants

### Weak Recommendations – 2\(^{nd}\)-Line

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>200-400</td>
<td>4.7</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>8% patch</td>
<td>10.6</td>
</tr>
<tr>
<td>(PNP)</td>
<td>(30-60 mins every 3 months)</td>
<td></td>
</tr>
<tr>
<td>Lignocaine</td>
<td>5% patch</td>
<td></td>
</tr>
<tr>
<td>(PNP)</td>
<td>(Max: 3 patches, up to 12 hours/day)</td>
<td></td>
</tr>
</tbody>
</table>
|               | (Demoted from 1\(^{st}\)-line due to “weak quality of evidence”)

### Weak Recommendations – 3\(^{rd}\)-Line

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Opioids</td>
<td>SR 180 mg Meq</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>individual titration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(13 trials in PNP used 10-120 oxycodone or 90-240 morphine; 10/13 +ve; max effectiveness 180mg morphine equivalent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(demoted from 1(^{st}) or 2(^{nd}) line – abuse potential, &amp; deaths, etc)</td>
<td></td>
</tr>
<tr>
<td>Botulinum A</td>
<td>50-200 units</td>
<td>1.9*</td>
</tr>
<tr>
<td>(PNP)</td>
<td>(Sub-cut every 3 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(*4 small RCTs; but one large unpublished RCT –ve)</td>
<td></td>
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</tbody>
</table>
**Recommendations against use:**
(Negative Trials &/or Safety Concerns)

1. **Weak recommendations against use:**
   - **Cannabinoids** (“negative results, potential misuse, diversion, & long-term mental health risks”)
   - **Valproate**

2. **Strong recommendations against use:**
   - **Levetiracetam**
   - **Mexiletine**

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**Medication Combinations**

**TCA + Gabapentinoid:**
- Nortriptyline + gabapentin (*The Lancet*; 10.10.09, pp 1252 – 61)
- Imipramine + pregabalin (*Pain*, May 2015, pp 958-66)

**SNRI + Gabapentinoid:**
- Duloxetine + pregabalin (*Pain*, July 2016, pp 1532–1540)

**Opioid +**
- Morphine + nortriptyline (*Pain*, August 2015, pp 1440-48)

See also:
The limited role of Opioids

1. Lack of evidence of long-term efficacy in Chronic pain
2. Tolerance and Physiological Dependence
3. Opioid Use Disorder
4. Risks of accidental overdose (US “opioid epidemic / crisis”)
5. Opioid-Induced Hyperalgesia
6. Difficult Withdrawal from Opioids
BPMC Opioid Guidelines (unchanged since 1999):

1. Don’t normally use strong opioids for chronic non-cancer pain
2. If we do, it’s normally methadone
3. Never prescribe at first visit – initiate opioids only after discussion at weekly case conference – IDT decision
4. We do not endorse the prescription of opioids for patients with a diagnosis of SUD – under A & D

Opioid Contract

Consider a signed opioid contract with the patient:

1. It is a trial – if it is not effective, it will be stopped. Starting a patient on morphine does not morally oblige us to continue it:
2. Patients don’t tell us what drug, & how many mg, to prescribe – the law specifies that that is our job.
3. Evidence of diversion / abuse → stop
4. “Effectiveness” normally needs an objective measure, e.g. improved function. E.g. a patient reporting that their pain “is much better, but it’s not good enough yet, because I’m still in agony & disabled by pain. So I need more” – is not evidence of efficacy, & thus not grounds for perpetual dose escalation
5. 100mg Morphine Equivalent / day will not be exceeded – risks, & lack of efficacy
6. No replacements for lost, eaten, stolen, or transmigrated scripts.
7. Random Urine Drug Screens – to see what is, & isn’t, present
8. One prescriber, one dispensing pharmacy
Fallacies, often implicit / sub-conscious, driving opioid prescribing & escalation:

“If all else fails, use morphine” because:

1. **It is our strongest analgesic, our gold standard. Wrong**: it *is* helpful for severe nociceptive or inflammatory pain (eg, post-op, post-traumatic), & in terminal malignant pain. But it is not the gold standard for neuropathic or nociplastic pain.

2. **The Fairy-Tale Fallacy (“they all lived happily ever after”): “There must be a fix.” Wrong**: Need to grapple with the Problem of Evil.

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**De-prescribing Opioids**


- Frank JW et al: “Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: Systematic Review”; *Ann Int Med*, 2017; doi:10.7326/M17-0598; published on-line 18.7.17

- Geller AS: “Patient & Public Safety Maximized by Rapid Opioid Taper”; *JAMA Internal Medicine*, June 2017; 895-6


- Darnall BD et al: “Patient-Centered Prescription Opioid Tapering in Community Outpatients With Chronic Pain”; *JAMA Internal Medicine*, online 19/2/18
Cannabinoids


- 91 publications with 104 studies were eligible (n = 9958 participants), including
  - 47 RCTs
  - 57 observational studies.
- 48 studies examined neuropathic pain,
- 7 studies examined fibromyalgia,
- 1 rheumatoid arthritis,
- 48 other CNCP (13 MS-related pain, 6 visceral pain, & 29 samples with mixed or undefined CNCP)


- 30% reduction in pain = 29% (cannabinoids) vs 26% (placebo),
- Number needed to treat to benefit (NNTB) for a 30% pain reduction: 24;
- 50% reduction in pain, 18% vs. 14%; no significant difference.
- Pooled change in pain intensity equivalent to 3mm on a 100mm visual analogue scale greater than placebo

- all-cause AEs = 81% vs. 66%;
- number needed to treat to harm (NNTH): 6.
- No significant impacts on physical or emotional functioning,
- Low-quality evidence of improved sleep, and patient global impression of change.

**Conclusions**

- “Evidence for effectiveness of cannabinoids in CNCP is limited.”
- “NNTB are high, and NNTH low, with limited impact on other domains.”
- “It appears unlikely that cannabinoids are highly effective medicines for CNCP.”

**CONCLUSIONS of recent SRs**

1. Weak evidence for efficacy of cannabinoids in neuropathic pain
2. No or insufficient evidence of efficacy in:
   - Chronic musculoskeletal pain
   - Headache disorders
   - Chronic visceral pain
   - Cancer pain
3. Few & low quality studies, providing insufficient evidence to gain FDA approval
4. Issue of adverse effects

*Whence the pressure for “medicinal cannabis”?*