Towards a Better Understanding of Chronic Pain

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The concept that

“pain is pain”

and that chronic pain is simply acute pain continuing for too long

is archaic and wrong
This misconception leads to:

1. General misunderstanding of what chronic pain is
2. Inadequate and inappropriate treatment of the pain
   a. incorrect medication –
   b. medication dose escalation
   c. overdosing of medication
   c. unnecessary special investigations
      radiology - cost!!
   d. unnecessary surgery or repeat surgery – especially spine surgery
3. General neglect of these patients:
   a. doctor doesn’t know what to do anymore
   b. patients get told it’s in their head – to psychologist or psychiatrist
   c. patients get told they must “learn to live with it”
   d. ‘change behaviour’.
Chronic Pain:

IS NOT:

- simply a symptom of another underlying condition
- “protective”
  DOES NOT
  Serve as warning
  Of underlying condition

IS:

- A medical entity, clinical condition
  And pathology in its own right
- Destructive,
  Serving no purpose at all
Nociceptive pain
Pain “with a cause” - an inflammatory or non-inflammatory response to a noxious stimulus

Neuropathic pain
Pain “without obvious cause” – initiated by a primary lesion or dysfunction in the peripheral or central nervous system

Nociceptive Pain

Pain “with a cause” - an inflammatory or non-inflammatory response to a noxious stimulus

Examples
- Pain due to inflammation
- Limb pain after a fracture
- Joint pain in osteoarthritis

Common Descriptors
- Aching
- Throbbing

Other characteristics
- Pain typically localised at site of injury
- Usually time limited, resolving when damaged tissue heals
- Responds to conventional analgesics

Neuropathic Pain

When nerves becomes damaged or sick, they stop working properly. They may send the wrong signal to the brain. Injured nerves might tell the brain that your foot is burning even when:

- you aren’t stepping on something hot
- or there is no toe at all!

Neuropathic pain is defined as "without obvious cause" – initiated by a primary lesion or dysfunction in the peripheral or central nervous system. 

Examples:
- Acute Shingles
- Phantom Pain
- Post-herpetic neuralgia
- Diabetic peripheral neuropathy
- Trigeminal neuralgia
- Postsurgical neuropathy
- Central Pain

Common descriptors:
- Burning
- Stabbing (lancinating)
- Tingling
- Radiating
- Hypersensitivity to touch or cold (allodynia)

Other characteristics:
- Responds poorly to conventional analgesics.
- Often in distribution of a specific nerve...

There are *Different* Types of Pain

**Nociceptive pain**
- Pain “*with a cause*” — an inflammatory or non-inflammatory response to a noxious stimulus

**Neuropathic pain**
- Pain “*without obvious cause*” — initiated by a primary lesion or dysfunction in the peripheral or central nervous system"¹

**Mixed**
- Pain with nociceptive and neuropathic components

**Examples²**
- Osteo-arthritis pain
- Fibromyalgia
- Back and leg

PPP = >25% of population in chronic pain clinics

Perkins and Kehlet  Anesthesiology 2000, 93; 1123 - 1133
Persistent Postoperative Pain - aka PPP

Pain that develops after surgery
Pain of at least two months duration
Other causes of pain have been excluded

Macrae BJA 2008

Postoperative pain that persists for 3-6 months after surgery

Kehlet et al Lancet 2006

Pain that persists after the time of healing

Bonica, The Management of Pain 1953
Discussion:
- 23% of the patients report chronic neuropathic pain measured at DN4 ≥ 4.
- 45% of the patients developed chronic (neuropathic and non-neuropathic) pain.

Conclusions:
Many patients suffer from chronic neuropathic pain after breast cancer surgery. All healthcare professionals (medical doctors, nurses and others) need to pay attention to this pain and treat it properly.
## Some incidences of PPP

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence</th>
<th>Author</th>
<th>Year</th>
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<tbody>
<tr>
<td>Post-cesarean</td>
<td>12.3%</td>
<td>Nikolajsen</td>
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<tr>
<td>Knee replacement</td>
<td>19.0%</td>
<td>Stanos</td>
<td>2001</td>
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<tr>
<td>Inguinal herniorraphy</td>
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<td>Mikkelsen</td>
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<tr>
<td>Mastectomy</td>
<td>52.0%</td>
<td>Macdonald</td>
<td>2005</td>
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<tr>
<td>Post thoracotomy</td>
<td>50 – 80%</td>
<td>Senturk</td>
<td>2002</td>
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</table>
Chronic Post Traumatic Pain

Orthopaedic trauma  11-48%  (77% in severe trauma)

Thoracic trauma  59%

Burn patients  30%

Spinal cord injuries  26-96%  (86%)

Traumatic brain injuries  40-75%

Radresa O. et al. J Trauma Acute Care Surg Volume 76, Number 4, 2014
PPP – Risk factors and predictors

- Type of surgery
- Genetic predisposition
- Female gender
- Young age
- Preoperative anxiety
- Negative psychosocial factors
- Obesity
- Pre-existing pain
- Inflammatory state
- Severe/poorly controlled postoperative pain
Pain Pathways

3 Neurons Involved in pain perception

1. Primary Neuron
   Transduction
   Peripheral Transmission

2. Secondary Neuron
   Central Transmission

3. Tertiary Neuron
   Central Transmission
   Perception

- Myelinated - Aδ
  ‘Fast Pain’

- UNmyelinated - C
  ‘Slow Pain’

Nociceptors

Brainstem

Cerebrum via Post. Thalamus
Modulation

Descending modulatory fibres

“Bi-directional”

Ease

Worsen or Cause

Opioids endo- and exo-

Minor injuries Expectation

Fear

Prolonged Pain
Pain Pathways

- Descending modulatory fibres - emotions, memory, etc.
- Interneuron inhibitory to pain fibres
- Dorsal root ganglia with all cell bodies of primary neurons
- Synapses between primary and secondary neurons
- C-fibres carrying pain from periphery
- A-fibres carrying touch, temperature, pressure and vibration from periphery
Chronic Pain:

Whatever the ORIGIN

NOCICEPTIVE  NEUROPATHIC

ULTIMATELY both lead to

altered pain processing
in dorsal horn of spinal cord (or brain)
due to physical (neuroplastic) changes there

giving BOTH types of chronic pain
a neuropathic element - Treatment!!!
Facilitated Pain Transmission
(gate open, central sensitization)

Mediated by two main mechanisms

NMDA Receptors

Interneurons
NMDA Receptors

N-methyl-D-aspartate

Where does NMDA occur physiologically in the body?

Nowhere!

It is a synthetic substance!
Used only in research to identify the receptors!
The NMDA receptors is actually a glutamate (excitatory) receptor!!
Figure of the NMDA receptor present the nervous system. Legend:
1. Cell membrane
2. Channel blocked by Mg$^{++}$ at the block site (3)
3. Block site by Mg$^{++}$
4. Hallucinogen compounds binding site
5. Binding site for Zn$^{++}$
6. Binding site for agonists(glutamate) and/or antagonist ligands(APV)
7. Glycosilation sites
8. Proton biding sites
9. Glycine binding sites
10. Polyamines binding site
11. Extracellular space
12. Intracellular space
Peripheral NMDA Receptors

In inflammation:
The number of NMDA receptors on peripheral nerve fibres increases

Sensitisation and Hyperalgesia

Inhibited by NMDA receptors antagonists:
In development - EXCITING!
Afferent Bombardment – Nociceptive or neuropathic positive feedback loop

Central NMDA Receptors

NMDA Receptor

AMPAR Receptor

NMDA Receptor

Mg++ block

μ-opioid receptor

μ/δ-opioid Receptor complex

mGlu R

PKC

↑ NO

↑ Superoxide

↑ IP3

Ca++

Ca++ - calmodulin

PKC

↑

Altered gene expression

PARS

ONOO -
So,

By afferent bombardment
(untreated acute pain),

BOTH noceptive and neuropathic pain,

If inadequately treated,

Lead to chronic pain
i.e changes in dorsal horn of spinal cord
(central sensitisation / wind up)

So both end up having a neuropathic element

See…. Duloxetine
Central NMDA Receptors

Inflammatory mediators
Blood borne

- NMDA Receptor
- AMPA Receptor
- mGlu R
- mGlu R
- PKC
- NO
- Superoxide
- NOS
- Ca++ - calmodulin
- Ca++
- IP3
- Mg++ block
- Remove Mg++ block
- Altered gene expression
- PARS
- ONOO -
Central NMDA Receptors

- Sensitivity of opiate receptors to opiates & tolerance

- Altered gene expression

- PARS

- NMDA Receptor

- AMPA Receptor

- mGlu R

- PKC

- Na⁺

- Ca²⁺

- IP3

- Superoxide

- NOS

- ONOO⁻
NMDA Receptors Antagonists

NMDA receptor antagonists inhibit hyperexcitability of spinal cord neurons induced by C-fiber stimulation.

Inhibited by NMDA receptors antagonists: Clinically available - MAGNESIUM
- Zinc
- ketamine
- dextromethorphan
- dextro-methadone
- amantidine (symmetrel)
- memantine (Ebixa)
Facilitated Pain Transmission (gate open, central sensitization)

Mediated by two main mechanisms

- NMDA Receptors
- Interneurons
The “Pain Gate” - can be either open or closed.

Interneurons can be killed by **Overstimulation** – Leaving the gate permanently open.
Interneurons can be killed by Overstimulation – Leaving the gate permanently open.

So, Interneurons are killed by Afferent bombardment.

Body’s own modulatory system – Stimulates interneurons.

Constant, severe untreated pain.

Over stimulation and death of interneurons.
Interneurons can be killed by **Overstimulation** – Leaving the gate permanently open

**Opiates Stimulate** interneurons

**Ever increasing doses** –

**Over stimulation and death of interneurons**

And hyperalgesia, tolerance to opiates.
Prolonged central sensitisation - can lead to:

Permanent alterations in central nervous system –
1. Death of inhibitory neurons
2. Replacement of them with new afferent excitatory neurons
3. Establishment of aberrant excitatory synaptic connections

Making chronic pain VERY difficult to treat sometimes

Need to treat acute pain adequately and appropriately
NOT just for patient comfort but to prevent or minimise chronic pain
Prolonged central sensitisation - can lead to:

Permanent alterations in central nervous system –
1. Death of inhibitory neurons
2. Replacement of them with new afferent excitatory neurons
3. Establishment of aberrant excitatory synaptic connections

Making chronic pain VERY difficult to treat sometimes

Need to treat chronic pain differently as an entity on its own and NOT simply apply acute pain therapy for a long time!!
Need to treat *chronic pain (noc & neuro)* differently as an entity on its own and NOT simply apply acute pain therapy for a long time!!

1. NMDA Blockers
2. Neuropathic pain drugs
   a. Gabapentin
   b. Pregabalin
   c. Carbamazepine
   d. Amitryptaline
   e. etc.
3. ? Opiates
4. Interventions
5. SCS and
Regional anesthesia?

- outcome at 6 months
- epidural anaesthesia for the prevention of PPP after thoracotomy (n=250)
- paravertebral block for breast cancer surgery (n=89)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favours regional</th>
<th>Conventional pain control</th>
<th>OR IV, Random, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
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<tr>
<td>1.1.1 Thoracotomy (epidural analgesia)</td>
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<td>Ju 2008</td>
<td>26</td>
<td>48</td>
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<td>Lu 2008</td>
<td>9</td>
<td>62</td>
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<td>Test for overall effect: $Z=3.69$ ($P=0.0002$)</td>
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1.1.2 Breast cancer surgery (paravertebral block)

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<th>Study or subgroup</th>
<th>Favours experimental</th>
<th>Favours control</th>
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</table>
Thank you
Traditionally:

Pain has been seen as a **symptom** of another underlying process / pathology which should go away once the underlying process / pathology has been eliminated.

This fits in with the definition of **Acute Pain** and has a protective function.
Traditionally:

Pain has been seen as a symptom of another underlying process/pathology which should go away once the underlying process/pathology has been eliminated.

But, clinically we have all seen:

1. Bad pathology – no or little pain.
3. Pathology eliminated – pain still present.
5. No apparent pathology at all – bad pain.

Something else going on!!?
Sometimes the pain is chronic:
by definition
if it persists for longer than 3 months
‘time definition’ is arbitrary

1. Sometimes chronic pain is present before 3 months have passed
2. Sometimes the mechanism for chronic pain is present from the outset.
3. Sometime the chronic pain happens “on its own” with no apparent causative factor
<table>
<thead>
<tr>
<th>Preoperative</th>
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<tbody>
<tr>
<td>Anxiety and Depression</td>
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<td>Catastrophizing</td>
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<td>Stressful life events</td>
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<td>Genes</td>
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<td>Impaired Pain Modulation</td>
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<td>Other pain states</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Sleep</td>
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<td>Stress</td>
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<table>
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<tr>
<th>Intraoperative &amp; post-operative healing period</th>
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<tbody>
<tr>
<td>Nerve injury</td>
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<tr>
<td>Tissue ischaemia</td>
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<tr>
<td>Surgical technique</td>
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<tr>
<td>Experience</td>
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<td>Anaesthetic technique</td>
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<tr>
<td>Pain facilitation or amplification</td>
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<tr>
<td>Pro-inflammatory states</td>
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<th>Delayed Post-operative period</th>
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<tr>
<td>Postoperative pain</td>
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<tr>
<td>Hyperalgesia</td>
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<td>Chemotherapy or radiation therapy</td>
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<tr>
<td>Repeat surgery</td>
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<tr>
<td>Psychosocial factors</td>
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Adapted form Wu and Raja, Lancet 2011
All sensation (including acute pain) originates at receptors in skin and tissues

“Nociceptors”
“Wind up”
Central sensitisation
↓
Physical changes in dorsal horn
Altered Pain Processing
↓
Facilitated pain transmission (gate open)
Increased perception of pain – hyperalgesia
and, even,
origination of new pain impulses

3. Tertiary Neuron
Central Transmission
Perception

Nociceptors
Pain Pathways
NMDA Receptors

New!

Late 1980’s

NMDA receptor antagonists inhibit hyperexcitability of spinal cord neurons induced by C-fiber stimulation.

Activation of NMDA receptors after tissue injury and inflammation enables facilitated processing in the spinal cord.
Interneurons can be killed by **Overstimulation** – Leaving the gate permanently open