Farmacologische behandeling van chronische atypische lage rugpijn

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31 year old woman with exacerbation of CNLBP.
Definitions

What is Pain?
What is Back Pain?
What is Low Back Pain?
What is Chronic Low Back Pain?
What is Chronic Non-specific Low Back Pain?

Medication in chronic LBP:
- according the type of pain - nociceptive, neuropathic or mixed.

Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components.
Morlion B.
I. Neurobiologie van pijnbanen  
II. Chronificatie van de pijn & centrale sensitizatietie  
III. Farmaca  
IV. Conclusie
Het ontstaan van pijn

Transductie
Activatie Nociceptoren
Nociceptieve stimuli

Transmissie
Voortgeleiding impulsen
Dorsale hoorn
Hersen

Modulatie
↓↓ of ↑↑↑ nociceptieve impulsen
(dorsale hoorn)

Perceptie
Pain Matrix
Fysiologische pijn
Which Transmitters / Receptors?

From Ringkamp M.et al. 2013
Glutamate receptors

**Ionotropic receptors**

- **AMPA** → noxious stimulation
  
  *exciting potential (EPSP) generated by glutamate at AMPA-R*

- **NMDA** → sensitisation after sustained activity in C-fiber afferent neurones.
  
  - Slower than AMPA.
  
  - Na+ and Ca++ voltage.

C-fiber afferent neurone: NMDA et AMPA.

Aδ afferent neurone: AMPA.

**Metabotropic glutamate receptors**

G-protein-coupled receptors (GPCR)

8 receptors identified; 2 excitatory & 6 inhibitory.

- Presynaptic control → glutamate release.

- Postsynaptic → nGluR1 → PKC → phosphorylation.

  AMPA, NMDA (Mg++ block is removed).
Pain Processing is Not a One-way Street

Before pain is experienced, the signals are modulated on different levels.
Afferent and Descending Pathways

Cortex

Descending Modulation

Periaqueductal Gray

Enkephalin
GABA

Locus Ceruleus
Noradrenaline

Nucleus Raphe Magnus

Serotonin (5-HT)

Nucleus Reticularis
Gigantocellularis

Nucleus Reticularis
Paragigantocellularis

Enkephalin

Medulla

Anterolateral Funiculus

Spinal Cord

SP, GABA, 5-HT, NE, ENK,
Neurotensin, ACH, DYN, CCK
VIP, CGRP, SOM, ADN, NPY,
GLU, NO, BOM, PGE

Enzyme Inhibitors
(ENK-ASE, ACH-ASE, NO-Synthase)

aP
Prostaglandins
Histamine
Serotonin
Bradykinin
Sensitizatie

→ decrease the threshold for activation of nociceptors

- **Perifere sensitizatie** (peripheral hypersensitivity)
  - Klinisch = **primaire hyperalgesie** (verhoogde pijnigevoeligheid in gebied van lesie).

- **Centrale sensitizatie** (central hypersensitivity)
  - Klinisch = **allodynie** (niet-nociceptieve prikkel wordt als pijnlijk ervaren)
  - Cruciale rol NMDA-receptor
  - Klinisch = **secundaire hyperalgesie** (verhoogde pijnigevoeligheid rond gebied van lesie)
Gebruikte farmaca

1. Paracetamol
2. NSAID’s
3. Opioiden
4. Antidepressiva
5. Anti-epileptica (anti-convulsants)
6. Flupirtine
7. Nefopam
8. LA (locale anesthetica)
9. alfa 2-agonisten
10. Anderen → Anti-NGF, Capsaicine (Qutenza), Cannabis,…
What are the obvious findings?
A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain

T. Kuijpers, M. van Middelkoop, S. M. Rubinstein
Eur Spine J (2011) 20:40–50
DOI 10.1007/s00586-010-1541-4

- The effectiveness of pharmacological interventions [i.e., non-steroid anti-inflammatory drugs (NSAIDs), muscle relaxants, antidepressants, and opioids] for non-specific chronic low-back pain (LBP).

- Existing Cochrane reviews.

- A total of 17 randomized controlled trials was included: NSAIDs (n = 4), antidepressants (n = 5), and opioids (n = 8).
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- No studies were found for muscle relaxants. The studies only reported effects on the short term (< 3 months). The overall quality of the evidence was low.

- NSAIDs and opioids seem to lead to a somewhat higher relief in pain on the short term, as compared to placebo, in patients with non-specific chronic low back pain.

- Both types of medication show more adverse effects than placebo.

- There seems to be no difference in effect between antidepressants and placebo in patients with non-specific chronic LBP.
Acetaminophen (Paracetamol)

- A well tolerated first-line pharmacotherapy for mild to moderate pain (Chou et al., 2007) but has limited efficacy (Zhang et al, 2010).

- Recommended by the American College of Physicians and the American Pain Society as a first line treatment for low back pain. (systematic review)

- MOA: not completely understood → analgesic & antipyretic.
  - COX-1?
  - TRPA1-receptors in the spinal cord; suppress the signal transduction from the superficial layers of the dorsal horn.
  - NMDA-antagonist?

- High dose long-term use is associated with hepatic toxicity (Watkins et al., 2006).

  → cave! Zaldiar + Dafalgan
A Cochrane review of 65 randomized controlled trials found evidence that NSAID’s are effective for the management of chronic low back pain, but effect sizes were indicative of only a small treatment effect. 
(Roelofs et al., 2008)

NSAID’s have better efficacy than acetaminophen but have well-known risks of gastrointestinal (Boers et al., 2007; Gabriel et al., 1991; Hippsley-Cox et al., 2005), cardiovascular (Antman et al., 2007; Caldwell et al., 2006; Hippsley-Cox & Coupland, 2005; Kearney et al., 2006; Motsko et al., 2006), renal (Barkin & Buvanendran, 2004; Evans et al., 1995) and other systemic adverse effects that increase with age, dose and duration of use.

different NSAID’s, including COX-II-inhibitors show similar efficacy in patients with chronic low back pain.

Drug interactions of NSAIDs with antihypertensives (ACE-inhibitors, diuretics), SSRI’s and corticosteroids are common.
(American Geriatrics Society, 2009; Malhotra et al., 2001; Tulner et al., 2008)
Opioids in non-cancer pain, major indications:

- **Chronic low back pain (CLBP)** of mechanical origin not responding to non-opioid agents or with neuropathic pain component.
- **Osteoarthritis (OA)** not responding to acetaminophen and contraindication (NSAIDs) and cyclooxygenase (COX)-2 inhibitors.
- **Neuropathic pain (NP)** not achieving adequate analgesia despite treatment with maximum doses of first- and second-line antineuropathic therapie.

*De Leon-Casasola The American Journal of Medicine, Vol 126, No 3A, March 2013*
Opioid analgesics or tramadol are an option when used judiciously in patients with acute or chronic low back pain who have severe, disabling pain that is not controlled (or is unlikely to be controlled) with acetaminophen and NSAIDs.
Opioids in neuropathic pain

Finnerup et al. Pain 2010; 150: 573
Opioids

Brain

- Opioids
- $\alpha_2$-$\delta$ ligands
- reuptake inhibitors/TCAs

Spinothalamic tract
- Ascending modulation
- Descending inhibition

Dorsal horn of spinal cord

- Local anesthetics
  - opioids
  - $\alpha_2$-$\delta$ ligands
  - reuptake inhibitors/TCAs
  - NSAIDs

Peripheral nerve

- Peripheral nociceptors

- Local anesthetics
  - capsaicin

- Local anesthetics
  - NSAIDs
  - opioids
  - capsaicin
Opioids; a double-edged sword?

- The Good: Analgesia.
- The Bad: Tolerance.
- The Ugly: OIH, Addiction.

**MOR Endomorphine ⇒ mu opioid receptor:**

- $\uparrow$ K+ efflux – hyperpolarisation
- $\downarrow$ cAMP (presynaptic)
- $\downarrow$ excitatory neurotransmitters release
opioid-induced side effects

- Maximum MED (Morphine Equivalent Dosis per day):
  100-200 mg (most guidelines 120 mg)

- MED 100 mg and > 90 days; critical

(Sullivan M. Pain 2013)
WHO analgesic ladder: stepwise approach

- by mouth
- by the clock
- by the ladder
- for the individual
- attention to side effects

KISS
Keep it Short and Simple
Muscle relaxants

Two main categories:

- **Antispasmodic**: decrease muscle spasm associated with painful conditions such as LBP.
  - BZD’s (e.g., Diazepam, Clonazepam): anxiolytics, sedatives, hypnotics, anticonvulsants, and/or skeletal muscle relaxants
  - Non-BZD’s.

- **Antispasticity**
  - Baclofen (Lioresal), Tizanidine (Sirdalud), Botuline toxine type A,
Are muscle relaxants effective in the treatment of chronic non-specific low back pain?

- Effective for short-term symptomatic relief but the adverse effects, especially the CNS adverse effects, require that they be used with caution.

- Trials are needed that evaluate if muscle relaxants are more effective than analgesics or non-steroidal anti-inflammatory drugs.

- In general, there is no evidence that any benzodiazepine is more effective than another if adequate dosage is given; however, pharmacokinetic differences between the drugs may be important considerations in prescription choice.

Antidepressants

- **Selective serotonin reuptake inhibitors (SSRI’s)**
  - Fluoxetine, Sertraline, Citalopram, Paroxetine, Fluvoxamine, Escitalopram,

- **Combined Serotonin-Norepinephrine Reuptake Inhibitors**
  - Dual Reuptake Inhibitors
  - Tricyclic antidepressants (TCA’s)
  - Selective serotonin-norepinephrine reuptake inhibitors (SNRI’s)

- **Monoamine Oxidase Inhibitors (MAO-I)**
Antidepressants

- **TCA’s analgesia: independent of their antidepressant properties**
  - Analgesia both in depressed and non-depressed patients.
    - Analgesia at lower doses.
    - Faster onset of action.
  - Activation of descending pain-inhibiting systems from the brain stem.
  - Serotonergic: from the raphe.
  - Noradrenergic from locus coeruleus.
• SNRI's:
  • Werken enkel op presynaptische re-uptake NA en 5HT
  • Geen effect op postsynaptische receptoren en ionkanalen → minder n.e. dan TCA's
  • Duloxetine (Cymbalta)
    • 1 keus bij diabetes PNP
    • Start 30 mg bij maaltijd ged 1 week, dan 60 mg/d
  • Venlafaxine (Efexor)
    • 37.5 mg/d ged 1 week
    • Progressieve optitratie naar 75 of 150 mg/d
**AD’s as analgesics: clinical practice guidelines**

**Neuropathic pain**
- Strong evidence: TCAs and SNRIs first line

**Fibromyalgia**
- Strong evidence for amitriptyline, duloxetine and milnacipran

**Musculoskeletal pain including low back pain**
- Moderate evidence for TCAs and SNRI

**Headache**
- Migraine prevention: moderate evidence: amitriptyline, venlafaxine // against clomipramine
- Chronic tension-type headache: strong evidence: amitriptyline.

**Cancer pain**

**Many others**: TMD, facial pain, IBS,…
Antidepressants for chronic non-specific low back pain.

Cochrane Database Syst Rev (1): Copyright © 2010
The Cochrane Collaboration.
Published by John Wiley & Sons, Ltd.

Urquhart DM, Hoving JL, Assendelft WWJJ, Roland M, van Tulder MW

There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic LBP. These findings do not imply that severely depressed patients with back pain should not be treated with antidepressants. Furthermore, there is evidence for their use in other forms of chronic pain.
AD’s for neuropathic pain

First-line:

**TCA’s:** amitriptyline, nortriptyline

**SNRI’s:** duloxetine, venlafaxine

**VGCC α2-δ ligand modulator:** pregabalin, gabapentin

**(Topical) lidocaine**

± Opioids

“Existing pharmacologic treatments for neuropathic pain are limited, with no more than 40–60% of patients obtaining partial relief of their pain.”
AD’s for neuropathic pain

Finnerup et al. Pain 2010
### Comparative potency of other TCAs when used at the equivalent NRI dose of amitriptyline

<table>
<thead>
<tr>
<th>Drug</th>
<th>NRI</th>
<th>Musc</th>
<th>α-1</th>
<th>$H_1$</th>
<th>5-HT$_{2A}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>1:1.5</td>
<td>2:1</td>
<td>1.5:1</td>
<td>8:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>5:1</td>
<td>1:10</td>
<td>1:10</td>
<td>1:25</td>
<td>1:15</td>
</tr>
<tr>
<td>Dosulepin</td>
<td>1:1.5</td>
<td>1:2</td>
<td>1:10</td>
<td>1:2</td>
<td>1:7</td>
</tr>
<tr>
<td>Imipramine</td>
<td>1:3</td>
<td>1:2</td>
<td>1:1</td>
<td>1:35</td>
<td>1:2</td>
</tr>
</tbody>
</table>
TCA’s: differences in adverse effects between TCAs

Least AE’s
Desimipramine
Nortriptyline
Imipramine
Doxepin
Amitriptyline

Most AE’s

Wall & Melzack’s Textbook of Pain, 6th edition 2013
TCA’s; practical points

- Evaluate need for sedation at night: yes: amitriptyline
- Dosing the same for most TCAs
- Usual analgesic dose range: 50-150 mg \(\text{(Dworkin et al. 2007)}\)
- Check ECG? (recommended >100mg)

- Amitriptyline (Redomex):
  - Start 10-25 mg at night, preference for immediate release
  - Titrate by 10-25 mg (every 3-7 days, or even slower 1-2 weeks)

- Nortriptyline (Nortrilen):
  - 10-25 mg up to 3 x day
  - 10 mg (ask the pharmacist for compunding)
Acupan (Nefopam)

- Centrally-acting non-opioid analgesic.
- Tab. 30 mg.
- Relief of moderate to severe pain.
- Third to half the potency and slightly less effective as an analgesic compared to morphine or oxycodone, fewer side effects, no respiratory depression, less abuse potential, useful as an alternative to opioids, or as an adjunctive treatment.
- Potentiating (analgesic-sparing) effect on morphine and other opioids by broadening the antinociceptive action of the opioid.

Acupan (Nefopam)

- Anticholinergic and sympathomimetic effects.
- Contraindications: convulsive disorders, MAO-inhibitors.
- Modes of action:
  - inhibition of 5-HT, DA and NEN reuptake (similar to AD’s)
  - VGSC-blocker.
  - histamine H3 receptors and glutamate.
- Side effects: sweating, dizziness, nausea, nervousness, dry mouth, light-headedness and urinary retention, vomiting, blurred vision, drowsiness, sweating, insomnia, headache.


Verleye, M; André, N; Heulard, I; Gillardin, JM (July 9, 2004). "Nefopam blocks voltage-sensitive sodium channels and modulates glutamatergic transmission in rodents". Brain Research 1013 (2): 249–55.
Flupirtine (Metanor)

• Niet-opioid, niet-NSAID centraal-werkend analgeticum
• NMDA-antagonisatie (via activatie K-kanalen)
• Bijkomende effecten:
  – Spierrelaxatie
  – Neuroprotectie (toekomst in Alzheimer, CJd, AIDS)
  – Anti-Parkinson effect (potentialisatie L-Dopa)
• Indicaties:
  – Musculoskelettale pijn (incl LBP, spatische toestanden)
  – Viscerale/ abdominale pijn
  – CSS → WAD, FMS,…
  – Migraine
  – Kankerpijn
Flupirtine (Metanor)

- ↓ neveneffecten in vgl met opioiden en NSAID's
- FK:
  - Metabolisatie in lever tot 1 actieve en 1 inactieve metaboliet
  - 72% renaal; 18% fecaal
- Dosis= 300-600mg/dag (caps 100mg)
- Interacties
  - ↑ hepatotoxisch potentieel van paracetamol (monitoring leverenzymen jaarlijks of per 6 maanden)
  - ↑ effect anti-vit-K.
- Niet op Belgische markt: UZA importeert uit Portugal.
Locale anesthetica

- **Lidocaine pleister 5% (Versatis)**
  - 700 mg/ 140 cm²
  - 3-voudige werking
    - Gecontroleerde vrijgave lidocaine
    - Koelend effect door hydrogel
    - Bescherming hypergevoelige huid (allodynie)
  - Indicaties= perifere neuropatische pijn
    → terugbetaling: PHN
  - Quasi geen systemische absorptie
  - Praktisch:
    - 12 uur ON/ 12 uur OFF
    - Min 4 weken therapie alvorens evaluatie effect mogelijk
    - Max 3 pleisters simultaan
Locale anesthetica

- **Lidocaine-infuus**

  - Systemisch membraan-stabiliserend effect (blokkade Na-kanalen) → ↓ ectopische actiepotentialen (ectopic pace-maker)
  - Praktisch:
    - 2 – 4 mg/kg IV over 2 – 3 uren → andere dosis?
    - EKG- monitoring, dagopname.
  - Absolute CI= 2de en 3de graad AV blok
**α₂-agonisten**

- **Clonidine (Catapressan), Dexmedetomidine (Dexdor)**
- Gebruik als analgeticum beperkt door sedatieve en vasodepressieve effecten.
- Werkingsmechanisme: stimulatie α₂-receptoren met activatie descenderend pijninhiberend systeem
- Activatie postsynaptische α₂-receptoren → ↑ K-influx met hyperpolarisatie cellmembraan en ↓ neuronale excitabiliteit
- Potentialisatie effect opioiden/ LA's
- **Praktisch:**
  - Clonidine 75-150 μg als adjuvans (perifeer/centraal blok)
  - Dexmedetomidine-infuus: 0,5 γ (μg/kg/uur) en progressief ↑
    (desensitisatie op INZO)
Descenderende inhibitie

α2 - agonisten
- Clonidine
- Dexmedetomidine
  - Grotere selectiviteit 1620:1 (vs. 300:1)
  - $T_{1/2}$: 2 à 3 uur

Essentiële rol in descenderende pijnmodulatie

Stimulatie $\Rightarrow$ veralgemeende analgesie
- Locus coeruleus
- Parabrachiale nucleus in medulla
- G-proteïne gemedieerde $K^+$ kanalen
Symptomatic Therapy of Chronic Low Back Pain

Diagnosis

Pharmacologic

Analgesics

Oral
Acetaminophen
Opioids
Tramadol
Tricyclic Antidepressants
Gabapentin
Benzodiazepines

Topical
Lidocaine

Anti-inflammatory

Oral
NSAID/COX2
w/wo PGE₂/PPI

Epidural
corticosteroid
injection

Nonpharmacologic

Patient education
Interdisciplinary rehabilitation
Exercise therapy
Acupuncture
Massage therapy
Spinal manipulation
Cognitive-behavioral therapy
Progressive relaxation

Other

Muscle relaxants
(baclofen, tizanidine)

Surgery

Every patient is different
Conclusie

- Ruim arsenaal farmaca ter beschikking voor behandeling chronische lage rugpijn
- Vaak combinatie (dosisreductie van iedere farmacon met minder kans op neveneffecten)
- Toediening op "time contingent basis" eerder dan op "pain contingent basis".

Multidisciplinaire therapie!
Multimodale therapeutische aanpak

Farmacotherapie

Reëducatie

Reïntegratie

Psychotherapie

Revalidatie
(Reactivatie)

Volgens de individuele patiënt...

Niet volgens een protocol...
Case

31 year old woman with exacerbation of CNLBP.

- She is diabetic with moderately decreased GFR (37 ml/min/1.73 m²).
- She is obese and suffers from sleep apnea + mild-to-moderate COPD.
- She is 16 weeks pregnant.
- *She is allergic to Paracetamol!*
Dank voor Uw aandacht!