Neuropathic pain treatment: Guidelines
HCN meeting Dec 2012

Troels Staehelin Jensen, MD, DMSc
Dept. of Neurology &
Danish Pain Research Center
Aarhus University Hospital, Denmark
Neuropathic Pain: Management

- Neuropathic pain and goals
- Pharmacological treatment
- Evidence and safety
- Combination therapy?
- Practical guide
Neuropathic Pain = Pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system (IASP, 1994).

Neuropathic Pain = Pain caused by a lesion or disease of the normal somatosensory system (IASP 2011).
Neuropathic Pain: Positive and Negative Sensory Symptoms

**Positive symptoms**
- Dysesthesia
- Sensory abnormalities and pain often co-exist
- Paresthesia
- Spontaneous pain
- Allodynia
- Hyperalgesia
- Dysesthesia
- Paresthesia

**Negative symptoms**
- Hypoesthesia
- Hypoalgesia
- Anaesthesia
- Analgesia

**Nervous system damage**

Inflammatory Pain: only Positive Symptoms

Inflammation or damage

Positive symptoms (increased peripheral input)

Spontaneous pain
  Allodynia
  Hyperalgesia
  Dysesthesia
  Paresthesia

Sensory abnormalities and pain often co-exist

# Chronic pains: Different etiologies

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Neuropathic</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>Nerve injury</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Neuropathies</td>
<td>Whiplash syndrome</td>
</tr>
<tr>
<td>Myositis</td>
<td>Plexopathy</td>
<td>Interstitial cystitis</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>Amputation</td>
<td>Irritable bowel disorder</td>
</tr>
<tr>
<td>Colitis</td>
<td>Trigeminal neuralgia</td>
<td>Persistent Idiopathic facial pains</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>Postoperative pain</td>
<td>Gulf War Syndrome</td>
</tr>
<tr>
<td>Migraine ?</td>
<td>MS</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>CRPS ?</td>
<td>Stroke</td>
<td></td>
</tr>
</tbody>
</table>
Complexity of pain:
Subjective and multidimensional
Multiple mechanisms
Associated phenomena.

Associated findings
- Neuroapthic pain
- Unable to work
- Lost selfesteem
- Depression
- Anxiety
- Sleep Distt.
- Other

Unidimensional measures

VA

No pain
Max pain

NRS
0 1 2 3 4 5 6 7 8 9 10

Mechanisms

Associated findings

Unidimensional measures

No pain
Max pain

VA

NRS
0 1 2 3 4 5 6 7 8 9 10
Neuropathic Pains: Multiple Mechanisms
Management of neuropathic pain:

Treatment Principles
- Reduce peripheral sensitisation
- Reduce ectopic activity
- Reduce activity in DRG
- Decrease central sensitisation
- Reduce central facilitation
- Increase central inhibition

Why combination therapies?
- Increase efficacy
- Reduce adverse actions
- Lower dosing

Gilron & Max 2005
Neuropathic Pain: Management goal

Treat cause of pain
High proportion with pain relief
Relevant pain relief
Sustained pain relief
Improvement in quality of life
Improvement in mood and sleep
Few and mild side effects
Low cost

Target different areas in order to reach the management goal
Neuropathic pain management: Decision making

PHN

Trigeminal neuralgia

Different etiology:
- Mechanisms differ (TN; spinal injury; PHN

Chronic conditions
- Long lasting diseases and long term treatment:

Vulnerable patient populations
- Elderly (PHN, TN, Diabetes)

Class of side effects
- CNS side effects severe in elderly
- GI side effects in certain patients

Neuropathy

Spinal cord injury

- Dull
- Squeezing
- Burning
- Pricking
Management of neuropathic pain: Reduce sensitization

**Treatment Principles**
- Reduce peripheral sensitisation
- Reduce ectopic activity
- Reduce activity in DRG
- Decrease central sensitisation
- Reduce central facilitation
- Increase central inhibition

**Pharmacological treatment**
- Stimulation therapy
- Physiotherapy
- Cognitive behavioral therapy

**Surgical** (other than stimulation)
Neuropathic Pain: Management

- Neuropathic pain and goals
- **Pharmacological treatment**
- Evidence and safety
- Combination therapy
- Practical guide
Neuropathic Pain: Pharmacology

- **Antidepressants**
  - Tricyclic antidepressants
  - SSRI
  - SNRI

- **Anticonvulsants**
  - Gabapentin
  - Pregabalin
  - Valproic acid
  - Topiramate
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoine
  - Lamotrigine
  - Lacosamide
  - Levetriacetam

- **Opioids**
  - Morphine
  - Oxycodone
  - Methadone
  - Tramadol

- **NMDA antagonists**
  - Memantine
  - Amantadine
  - Dextromethorphan
  - Riluzole

- **Cannabinoids**

- **Topicals**
  - Lidocaine
  - Capsaicin (0.075%, 8%)

- **Mexiletine**

- **Neurotrophic factors** (Prosaptide)

- **NGF**

- **BTX**

- **Glycine antagonist**

- **Nitrates**

- **Nic ACH-Rec**

- **NK1 rec antagonist**
Antidepressants:
Modulation by TCA

TCA blocks:
- 5-HT; NA transporters
- NMDA receptors
- Na⁺ channels
- Cholinergic receptors
- α-adrenergic receptors
- Ca²⁺ channels
- Stim. effect on opioid receptors

Pain conditions
- Painful polyneuropathy
- Painful diabetic neuropathy
- Post-herpetic neuralgia
- Peripheral nerve injury pain
- Mixed neuropathic pain
- Post-stroke pain

Compounds
- Amitriptyline
- Imipramine
- Clomipramine
- Desipramine
- Nortriptyline
- Maprotilin
- Venlafaxine
- Duloxetine
- Citalopram
- Escitalopram
- Fluoxetine
- Paroxetine
- Bupropion
# Neuropathic Pain:
Pharmacology of antidepressants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reuptake 5-HT</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Reuptake NA</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reuptake DA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>a-adrenergic block</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>H1-histamine block</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Muscarinic-cholinergic block</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NMDA block</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Na⁺ ion block</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SDRI = selective dopamine reuptake inhibitors; SNRI = Serotonin/noradrenaline reuptake inhibitors; SSRI = Selective serotonin reuptake inhibitors; TCA = Tricyclic antidepressants.
Antidepressants in Painful Polyneuropathy

Anticonvulsants:
Modulation by Ca\(^{++}\) channel binding

- N-type Ca\(^{++}\) channel antagonist reduces hypersensitivity.
- \(\alpha_2\delta\) subunits upregulated in DRG and central terminals in NP.
- \(\alpha_2\delta\)-binding agents reduces NP

Pain conditions:
Painful diabetic neuropathy
Painful neuropathy
HIV neuropathy
Guillain-Barré syndrome
Postherpetic neuralgia
Central poststroke pain
Central spinal cord injury pain
Mixed neuropathic pain

Compounds:
Gabapentin
Pregabalin
Anticonvulsants: Modulation by Na⁺-blockers

- At least 10 different voltage-gated Na⁺ channels
- TTX-R Na⁺ channels expressed by small fibers
- Nav1.3 and Nav1.7 upregulated; Nav1.8, and Nav1.9 downregulated in some NP

NP Pain conditions:
- Painful diabetic neuropathy
- Painful neuropathy
- HIV neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
- Central poststroke pain
- Mixed neuropathic pain

Compounds:
- Lacosamide
- Lamotrigine
- Topiramate
- Levetiracetam
- Carbamazepine
- Oxcarbazepine
- Phenytoin
Opioid Analgesics:
Modulation by opioids

1. Opioid receptors expressed on: primary afferents, central terminals postsynaptic neurons
2. Loss of presynaptic opioid receptors in NP
3. CCK expression increased in spinal cord after nerve injury

Pain conditions:
Painful diabetic neuropathy
Postherpetic neuralgia
Postamputation pain
Mixed neuropathic pain

Compounds
Morphine
Oxycodone
Levorphanol
Methadone

Adverse effects
Physical dependence
Addiction/Abuse
Tolerance
Sedation, confusion, dizziness, dysphoria, nightmares
Constipation, nausea, Urinary retention
Immunologic changes
Opioids:

1. Opioid receptors expressed on: primary afferents, central terminals postsynaptic neurons
2. Loss of presynaptic opioid receptors in NP
3. CCK expression increased in spinal cord after nerve injury

Pain conditions:
- Painful diabetic neuropathy
- Postherpetic neuralgia
- Postamputation pain
- Mixed neuropathic pain

Compounds
- Morphine
- Oxycodone
- Levorphanol
- Methadone
New treatments for NP: Capsaicin for neuropathy pain
Depletes SP and other transmitters from terminals
Topical capsaicin (8% 640mcg/cm²)

Painful HIV neuropathy

Simpson et al. Neurology 2008

NNT 6.5
Study:
- Randomized DBC parallel study
- 206 PHN pts 8% capsaicin cream
- 196 PHN pts 0.04% capsaicin cream

Adverse effect:
- Transient increase in BP
- Pain at application site
- Erythema

Backonja et al. 2008
Newer treatments in NP: Botox

Botox antinociceptive properties

**Reduced release of SP**
(Purkiss et al. 2000)

**Regulation of CGRP release**
(Durham et al. 2004)

**Reduced release of glutamate**
(Cui et al. 2004)

**Inhibition of vanilloid receptor**
(Morenilla-Palao et al. 2004)
Neuropathic Pain: Management

- Neuropathic pain and goals
- Pharmacological treatment
- Evidence and safety
- Combination therapy
- Practical guide
Systemic NeP treatment evidence

Based on NNT in neuropathic Pain: NNT ≥ 3 for all compounds

Need for:
1. New and better treatments
2. Better use of existing treatments
3. Reduce side effects
Neuropathic pain management:
Adverse actions / contraindications

<table>
<thead>
<tr>
<th></th>
<th>(\alpha_2\delta)-binding agents</th>
<th>Na(^+) blocking agents</th>
<th>TCA</th>
<th>SNRI</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Sedation Ataxia Dizziness Mental change Memory change Headache Weight gain edema flatulence</td>
<td>Sedation Ataxia Dizziness Mental change Memory problem Headache Weight gain edema Hyponatraemia</td>
<td>Sedation Dizziness Mental change Weight gain Dry mouth Hypotension Sweating Palpitations Constipation Blurred vision Sexual dysf.</td>
<td>Sedation Dizziness Mental change Nausea Weight loss Hypertension Sweating Diarrhoea Sexual dysf.</td>
<td>Dizziness Agitation Mental change Nausea Weight change Tachycardia Sweating Sexual dysf.</td>
</tr>
<tr>
<td><strong>Contra-indication</strong></td>
<td>None</td>
<td>AV-block Porphyria MAO inhibitors</td>
<td>AV-block Cardiac insufficiency Recent MI MAO inhibitors</td>
<td>Reduced Liver function Reduced Kidney function MAO inhibitors</td>
<td>Reduced Liver function Reduced Kidney function MAO inhibitors</td>
</tr>
</tbody>
</table>
Can we based on NNT/NNH values determine the preference of drugs for treating Neuropathic pain

**Conclusion:**
Drug Preference
Z > Ref = Y < X
Painful polyneuropathy: NNT and NNH

NNT/NNH for opioids look better than TCA pregabalin and gabapentin, but is that true?
Postherpetic Neuralgia: NNT and NNH

- TCA
- Opioids
- Tramadol
- Pregabalin
- Gabapentin
- Valproate
- NMDA antag
- Topical Capsaicin
- NGX Capsaicin
- Topical Lidaocaine

NNT

- TCA
- Opioids
- Tramadol
- Pregabalin
- Gabapentin
- Valproate
- NMDA antag
- Topical Capsaicin
- NGX Capsaicin
- Topical Lidaocaine

NNH

- TCA
- Opioids
- Tramadol
- Pregabalin
- Gabapentin
- Valproate
- NMDA antag
- Topical Capsaicin
- NGX Capsaicin
- Topical Lidaocaine

Finnerup et al. 2010
Neuropathic Pain: Management

- Neuropathic pain and goals
- Pharmacological treatment
- Evidence and safety
- Combination therapy
- Practical guide
Combination of treatment:
Modulation by opioids, $\alpha_2\delta$-binding agents or Noradrenaline

1. Opioid receptors expressed on: primary afferents, postsynaptic neurons in CNS
2. $\alpha_2\delta$-binding agents located on primary afferent and neurons in CNS

Pain conditions:
Painful diabetic neuropathy
Postherpetic neuralgia

Compounds
Morphine
Gabapentin/pregabalin
NeP combination treatments: Is there anything to gain?

- Randomised, double-blind
- Placebo-controlled
- 4-way cross-over
- Single centre
- 5-week treatment periods
- GABA 3200 mg
- MORP 120 mg
- GABA 2400 mg + MORP 60 mg

\[ \text{NNT}_{\text{gabapentin}} = 3.2 \ (2.0 - 8.9) \]
\[ \text{NNT}_{\text{morphine}} = 2.0 \ (1.5 - 3.2) \]
\[ \text{NNT}_{\text{combination}} = 2.1 \ (1.5 - 3.4) \]

Neuropathic Pain: Management

- Neuropathic pain and goals
- Pharmacological treatment
- Evidence and safety
- Combination therapy
- **Practical guide**
Pharmacological treatment of NP:
What do we need to know before start?

Clinic:
- Diagnosis
- Types of pain
- Impact
- Intensity of pain
- Adverse effects
- Mood
- Sleep
- Former Treatments
  - type
  - dosing
  - duration
- Contradindications
- Endpoint: PGIC
- Cost
Ideal Criteria for a pain relieving treatment

Consistent outcome from high-quality trials
High degree of pain relief
Sustained pain relief
Few and mild side effects
Effect on other parameters than pain
Low cost

Which parameter is most important?
Neuropathic pain: Pharmacological algorithm

1. **Peripheral**
   - Topical lidocaine, topical capsaicin, opioids

2. **Central**
   - Tramadol, opioids, Oxcarbazepine, lacosamide, lamotrigine

3. **TCAs**
   - SNRI

4. **α-2-δ agents**

5. **Cause**, **Comorbidity**, **Contraindication**, **Cost**
EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2009 revision

N. Attal\textsuperscript{a,b}, G. Cruccu\textsuperscript{a,c}, R. Baron\textsuperscript{a,d}, M. Haanpää\textsuperscript{a,e}, P. Hansson\textsuperscript{a,f}, T. S. Jensen\textsuperscript{a,g} and T. Nummi\textsuperscript{a,h}

<table>
<thead>
<tr>
<th>D.P. N.</th>
<th>PHN</th>
<th>HIV</th>
<th>Central</th>
<th>TN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td>TCA, Gbp, Prgb, SNRI Tramadol, opioids</td>
<td>TCA, Gbp, Prgb, opioids Caps 8%</td>
<td>Caps 8% Smoked cannabis</td>
<td>Prgb (SCI) Cannab (MS)</td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td>Tramadol, lidoc. topic caps. topic (valp)</td>
<td>Lamotrigine</td>
<td>Prgb TCA lamotrigine Gbp</td>
<td>OXZ</td>
</tr>
<tr>
<td><strong>1\textsuperscript{st} line</strong></td>
<td>Gbp, Prgb., TCA,</td>
<td>Gbp Prgb, TCA Lidoc.topic.</td>
<td>Caps 8%</td>
<td>Prgb, TCA Gbp</td>
</tr>
<tr>
<td><strong>2\textsuperscript{nd} line</strong></td>
<td>SNRI, Lamotr., Tramadol, opioids</td>
<td>Caps. topic Tramadol opioids</td>
<td>Cannb. Lamotrigine opioids</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Attal et al. 2006, 2010
<table>
<thead>
<tr>
<th>Drug</th>
<th>Start dose</th>
<th>Maximum dose</th>
<th>Documented Effect</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Start: 300 mg/day</td>
<td>Max: 3600 mg/day</td>
<td>PHN, PDN, MNP</td>
<td>Sedation, dizziness, edema</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Start: 25 mg/day</td>
<td>Max: 600 mg/day</td>
<td>PHN, PDN, MNP CP</td>
<td>Sedation, dizziness, edema</td>
</tr>
<tr>
<td>TCA</td>
<td>Start: 25 mg/day</td>
<td>Max: 75-150 mg/day</td>
<td>PHN, PDN, CP, MNP</td>
<td>Cardiac disturbances, ACH side effects, sedation</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Venlafaxine —</td>
<td>Max: 225-375 mg/day</td>
<td>PNP and PDN</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Start: 37.5 mg</td>
<td>Max: 225-375 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duloxetine —</td>
<td>Start: 60 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>Carbazepine,</td>
<td>Max: 300 mg/day</td>
<td>TN</td>
<td>Sedation, dizziness, ataxia, low S-Na⁺</td>
</tr>
<tr>
<td></td>
<td>oxcarbazepine</td>
<td>(1/3 higher dose for OXC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadon</td>
<td>Start: 50 mg/day</td>
<td>Max: 400 mg/day</td>
<td>PN</td>
<td>Sedation, dizziness, constipation</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Start: 25 mg /day</td>
<td>Max: 400-600 mg/day</td>
<td>TN, CPSP</td>
<td>Sedation, tremor, rash</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Start: 5-10 mg/day</td>
<td>titrate substitute with long-acting O Max: variable</td>
<td>PHN, PDN, CPSP</td>
<td>Sedation, dizziness, tolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>drug abuse</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Lidocaine</td>
<td>Max: variable</td>
<td>PHN, Traumatic nerve injury</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td></td>
<td>medicated patch</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>Capsaicin</td>
<td>0.075% and 8%</td>
<td>PHN, PDN, HIV</td>
<td>Pain</td>
</tr>
</tbody>
</table>
Thanks to all collaborators at DPRC:
Birgitte Brandsborg, Gitte Lau Pedersen, Lene Vase, Lone Nikolajsen, Anders
D Kristensen, Hanne Gottrup, Nanna Finnerup, Cathrine Baastrup, Henriette
Klit, Lise Wentzel, Karen Lund, Jeantte Springer, Emilia Horjales, Simon
Houratien Astrid Terkelsen, Helle O. Andersen, Anne Hansen, Lone
Knudsen, Casper Skau-Madsen, Kaare Meier, Paal Karlsson