Neuropathic Pain
- Pathophysiologic Mechanism-based Pharmacological Therapies

Jijun Xu, MD, PhD
Department of Pain Management, Anesthesiology Institute
Department of Inflammation and Immunity, Lerner Research Institute
Cleveland Clinic
Objectives

• To characterize and diagnose neuropathic pain
• To describe and differentiate the mechanisms underlying neuropathic pain
• To formulate mechanism-based pharmacological therapies for different neuropathic pain
DEFINITION AND ASSESSMENT OF NEUROPATHIC PAIN
International Association for the Study of Pain (IASP)

Definition of Neuropathic Pain

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

- **Central neuropathic pain:**
  - Brain: stroke, PD, MS
  - Spinal cord: myelopathy, SCI

- **Peripheral neuropathic pain:**
  - Spinal radiculopathy: cervical, thoracic, lumbar
  - DPN, PHN, CRPS, peripheral nerve entrapment, chemo-, radiation
  - Inflammatory demyelinating, HIV
  - Idiopathic sensory neuropathy
  - Nutrition-deficiency, toxin-exposure, or alcohol-related neuropathy

http://www.iasp-pain.org
Characteristic manifestation of neuropathic pain

• Spontaneous pain
  – **Continuous** pain: burning, squeezing, pressure
  – **Paroxysmal** pain: electric shock-like, stabbing

• Evoked pain
  – **Hyperalgesia**: painful stimulus e.g. pinprick-evoked.
  – **Allodynia**: nonpainful stimulus e.g. cold-, brush- or pressure-evoked.
  – **Hyperpathia**: abnormally painful reaction to a stimulus, especially a repetitive stimulus.

• **Paresthesia and dysesthesia**: tingling, pins, and needles – “abnormal”
  – Spontaneous or evoked
  – Not unpleasant or unpleasant

• The most common three:
  – ongoing burning pain (65.4%),
  – paroxysmal electric shock-like pain (57%),
  – brush-evoked pain (54.9%)

Assessment of Neuropathic Pain:

• Screening tools
  – The Leeds Assessment of Neuropathic Symptoms and Signs
  – The Neuropathic Pain Questionnaire and the NPQ short form
  – Neuropathic Pain Diagnostic (DN4) Questionnaire

• Clinical examinations

• Laboratory tests

• Recommendations from Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP)

## Screening tools for Neuropathic Pain: The Leeds Assessment of Neuropathic Symptoms and Signs

### LANSS Pain Scale

<table>
<thead>
<tr>
<th>Symptom / Sign</th>
<th>Score for “yes”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the pain feel like strange unpleasant sensations? (e.g. pricking, tingling, pins/needles)</td>
<td>5</td>
</tr>
<tr>
<td>Do painful areas look different? (e.g. mottled, more red/pink than usual)</td>
<td>5</td>
</tr>
<tr>
<td>Is the area abnormally sensitive to touch? (e.g. lightly stroked, tight clothes)</td>
<td>3</td>
</tr>
<tr>
<td>Do you have sudden unexplained bursts of pain? (e.g. electric shocks, ‘jumping’)</td>
<td>2</td>
</tr>
<tr>
<td>Does the skin temperature in the painful area feel abnormal? (e.g. hot, burning)</td>
<td>1</td>
</tr>
<tr>
<td>Exam: Does stroking the affected area of skin with cotton produce pain?</td>
<td>5</td>
</tr>
<tr>
<td>Exam: Does a pinprick (23 GA) at the affected area feel sharper or duller when compared to an area of normal skin?</td>
<td>3</td>
</tr>
</tbody>
</table>

0 - 12 = likely nociceptive, Score > 12 likely neuropathic

Screening tools for Neuropathic Pain: The Neuropathic Pain Questionnaire

Neuropathic Pain Questionnaire

In order to assess and treat your pain problem, we need to thoroughly understand just exactly what type of pain you have, and how it may or may not change over time. You may have only one site of pain, or you may have more than one.

Please name the site of pain which is most severe or disturbing for you (eg, arm, foot, etc):

For all of the following questions, please rate your pain at the site you just listed. Please use the space below to describe your pain in your own words:

Please use the items below to rate your pain as it usually feels. Indicate a number which represents your pain on each scale. For example, if you have no burning pain, you would rate the first item “0”. If you have the worst burning pain imaginable, you would rate it “100”. If neither of those fit your pain because it is in between, choose a number which fits your pain.

1. Burning Pain
   0 → 100
   No Burning    Worst Burning    Pain Imaginable
   Please rate your usual pain:

2. Overly Sensitive to Touch
   0 → 100
   No       Worst
   Oversensitivity    Oversensitivity    Imaginable
   Please rate your usual pain:

3. Shooting Pain
   0 → 100
   No Shooting    Worst Shooting    Pain Imaginable
   Please rate your usual pain:

4. Numbriness
   0 → 100
   No       Worst Numbriness
   Numbriness    Imaginable
   Please rate your usual pain:

5. Electric Pain
   0 → 100
   No Electric    Worst Electric    Pain Imaginable
   Please rate your usual pain:

6. Tingling Pain
   0 → 100
   No Tingling    Worst Tingling    Pain Imaginable
   Please rate your usual pain:

7. Squeezing Pain
   0 → 100
   No Squeezing    Worst Squeezing    Pain Imaginable
   Please rate your usual pain:

8. Freezing Pain
   0 → 100
   No Freezing    Worst Freezing    Pain Imaginable
   Please rate your usual pain:

9. How unpleasant is your usual pain?
   0 → 100
   Most        Unpleasant
   Please rate your usual pain:

10. How overwhelming is your usual pain?
    0 → 100
    Most Over-
    whelming    Pain Imaginable
    Please rate your usual pain:

Scoring Worksheet:

Instructions: For each of the twelve items below, copy the subject’s score into the first column. Multiply by the coefficient in the second column, and write the product in the third column. Total all the figures in the third column, including the constant. The resulting total represents the discriminant function score. Subjects with scores below 0 are predicted to have non-neuropathic pain, while those with scores at or above 0 are predicted to have neuropathic pain.

8. Freezing Pain
   0 → 100
   No Freezing    Worst Freezing    Pain Imaginable
   Please rate

9. How unpleasant is your usual pain?
   0 → 100
   Most        Unpleasant
   Please rate

10. How overwhelming is your usual pain?
    0 → 100
    Most Over-
    whelming    Pain Imaginable
    Please rate

We are also interested in learning what circumstances cause changes in your pain. Please write the number that indicates the amount you experience each of the following:

11. Increased pain due to touch
    0 → 100
    No Increase   Greater
    At All       Increase
    Pain Imaginable
    Please rate

12. Increased pain due to weather changes
    0 → 100
    No Increase   Greater
    At All       Increase
    Pain Imaginable
    Please rate

Krause et al., Clinical Journal of Pain. 2003; 19(5):306-314,
Screening tools for Neuropathic Pain: The Neuropathic Pain Questionnaire (NPQ) – Short Form

**NEUROPATHIC PAIN QUESTIONNAIRE—Short Form**

In order to assess and treat your pain problem, we need to thoroughly understand just exactly what type of pain you have, and how it may or may not change over time. You may have only one site of pain, or you may have more than one.

Please name the site of pain which is most severe or disturbing for you (e.g., arm, foot, etc):

For all of the following questions, please rate your pain at the site you just listed.

Please use the space below to describe your pain in your own words as well:

Please use the items below to rate your pain as it usually feels. Indicate a number which represents your pain on each scale. For example, if you have no tingling pain, you would rate the first item “0.” If you have the worst tingling pain imaginable, you would rate it “100.” If neither of those fits your pain because it is in between, choose a number which fits your pain.

1SF, Tingling Pain

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
|---|---|---|---|---|---|---|---|---|---|---
| No Tingling | Pain | Worst Tingling | Pain Imaginable | Please rate your usual pain: ________ |

2SF, Numbness

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
|---|---|---|---|---|---|---|---|---|---|---
| No Numbness | Sensation | Worst Numbness | Imaginable | Please rate your usual pain: ________ |

We are also interested in learning what circumstances cause changes in your pain. Please write the number that indicates the amount you experience each of the following:

3SF, Increased pain due to touch

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10
|---|---|---|---|---|---|---|---|---|---|---
| No Increase | At All | Greatest Increase | Imaginable | Please rate your usual pain: ________ |

**Canonical Discriminant Function Coefficients and Structure Coefficients**

<table>
<thead>
<tr>
<th>Item</th>
<th>Canonical Discriminant Function Coefficient</th>
<th>Structure Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1SF, Numbness</td>
<td>.017</td>
<td>.819</td>
</tr>
<tr>
<td>2SF, Tingling Pain</td>
<td>.015</td>
<td>.828</td>
</tr>
<tr>
<td>3SF, Increased Pain due to Touch</td>
<td>.011</td>
<td>.569</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.302</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL DISCRIMINANT FUNCTION SCORE:** ________

**Check one of the following boxes:**

| Discriminant Function Score at or Above 0: | Predicts | Neuropathic Pain |
| Discriminant Function Score Below 0: | Predicts | Non-Neuropathic Pain |

**Neuropathic Pain Questionnaire-Short Form.**
Backonja, Misha-Miroslav; Krause, Steven

# Screening tools for Neuropathic Pain: Neuropathic Pain Diagnostic (DN4) Questionnaire

## DN4 Questionnaire

<table>
<thead>
<tr>
<th>Symptom / Sign</th>
<th>Yes = 1</th>
<th>No = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the pain have the following characteristic?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the pain have the following characteristic?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the pain have the following characteristic?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electric shocks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pins &amp; needles?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Decrease in touch sensation (soft brush)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Decrease in prick sensation (von Frey hair #13)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allodynia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Does movement of a soft brush in the area cause or increase pain?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 – 3 = likely nociceptive pain; ≥4 = likely neuropathic pain

# Screening tools for Neuropathic Pain

## Table 2. Validity and Reliability of the Different Neuropathic Pain Scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Scoring</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive Value (%)</th>
</tr>
</thead>
</table>
| LANSS<sup>15</sup> | 7-item scale: 5 questions (unpleasant skin sensations, appearance, increased sensitivity to touch, electric-shock, or hot/burning sensations), 2 questions (sensory testing for allodynia and altered pinprick threshold) | Maximum score: 24  
Neuropathic: > 12  
Nociceptive: < 12 | 85               | 80               | 82                |
| NPQ (short-form)<sup>16</sup> | 3-items on a 0–100 mm scale (numbness, pain, increased pain from touch) | Neuropathic: At or above 0  
Non-neuropathic: Below 0 | 64.5           | 78.6             | 73                |
| DN4<sup>17</sup> | 4 Questions (characteristics of pain, symptoms, presence of hypesthesia, effect of brushing) | Maximum: 10  
Neuropathic pain: 4 or higher | **82.9** | **89.9** | **86**           |

LANSS, Leeds Assessment of Neuropathic Pain Symptoms and Signs; NPQ, Neuropathic Pain Questionnaire; DN4, Douleur Neuropathique 4.

Jongen JL et al., *Pain Practice* 2014 (14); 3: 283–295
Clinical examination of somatosensory functions

• Sensory testing is the most important part of clinical examination and includes testing of touch, pinprick, vibration, cold and warmth.
  – Tactile sense is assessed by a piece of cotton wool
  – Pinprick sense by a wooden cocktail-stick
  – Vibration sense by a 128-Hz tuning fork
  – Thermal sense by warm and cold objects (e.g., metal thermorollers)

• Clinical examination can never prove any pain to be of neuropathic origin, it can only provide supporting evidence for altered function of the nervous system.

• Pain in a region with nerve injury is not necessarily all of neuropathic origin, and a nerve injury may also give rise to, for example, altered muscle tone or movement pattern and a concomitant nociceptive pain.

Laboratory testing for neuropathic pain: Psychophysiological, Neurophysiological, and quantitative methods

Recommendations from NeuPSIG on NP assessment

- Screening questionnaires are suitable for identifying potential patients with neuropathic pain.

- Clinical examination, including accurate sensory examination, is the basis of neuropathic pain diagnosis.

- For more accurate sensory profiling, quantitative sensory testing is recommended for selected cases in clinic, including the diagnosis of small fiber neuropathies and for research purposes.

- Skin biopsy to measure the intraepidermal nerve fiber density should be performed in patients with clinical signs of small fiber dysfunction.

- Assessment of sleep, mood, functional capacity and quality of life are recommended.

PATHOPHYSIOLOGICAL MECHANISMS OF NEUROPATHIC PAIN
Pathophysiology of Neuropathic Pain

• Peripheral sensitization
  – Upregulation of NGF, ion channels, α-adrenoceptors, TRPV receptors
  – Ectopic discharge
  – Sympathetic sprouting

• Central sensitization
  – NMDA receptor activation
  – GABA disinhibition
  – Microglia and astrocytes

• Functional deafferentation

• The Pain Genetics
Mechanisms of Neuropathic Pain: the primary afferent pathway

Baron R, Nature Clinical Practice Neurology 2006. 2, 95-106
Mechanisms of Neuropathic Pain: Peripheral sensitization

Mechanisms of Neuropathic Pain: Central sensitization

Central sensitization: NMDA receptor

Central sensitization: Microglia activation

Marchand et al., *Nature Reviews. Neuroscience* 2005. 6, 521-532
Selective CB2 receptor agonist blocks paclitaxel-induced peripheral neuropathy by inhibiting spinal cord microglia activation in rats

Naguib and Xu et al., *Anesth Analg.* 2012;114(5):1104-20
CX3CR1 and microglial activation in an CRPS model

Mechanisms of Neuropathic Pain: Central sensitization

Mechanisms of Neuropathic Pain: Deafferentation

- Complete or partial interruption of afferent nerve impulses
- Spinal cord injuries, peripheral nerve injuries, brachial plexus avulsions, limb amputations, and anesthesia dolorosa
- Spinal segmental loss of 1° afferent neurons may lead to:
  - Sprouting to fill vacant synapse
  - Dorsal horn neuron fire and paroxysmal bursting discharge
  - Central reorganization

Mechanisms of Neuropathic Pain: Pain Genetics

• Neuropathic pain gene: hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channel
  – Deleting the HCN2 gene abolished neuropathic pain but not acute pain in mice
  – Blocking or genetically deleting HCN2 channels in small nociceptive neurons suppressed diabetic-associated mechanical allodynia in mice
    – Tsantoulas C et al., *Science Translational Medicine* Sep 2017

• Single nucleotide polymorphism
  – Potassium channel subunit: Costigan M et al., Brain 2010
  – SCN9A: Reimann F et al., *PNAS* 2010

• Gain-of-function mutation of SCN9A for Nav1.7 → erythromelalgia and paroxysmal extreme pain disorder

• Genes contribute to neuron excitability and neuroinflammation
  – Wang H et al., *Neuroscience* 2002
Possible Mechanisms underlying different neuropathic symptoms

• Spontaneous pain
  – Ectopic discharge in C fibers
  – Changes in VG Na channel
  – Sympathetic sprouting

• Paresthesia
  – Changes in VG Na channel, ectopic discharge

• Hyperalgesia
  – Peripheral sensitization
  – Central sensitization

• Allodynia
  – Phenotypic switch in Aβ fibers: synthesis and release of substance P
  – Sprouting of Aβ fibers

Woolf CJ et al., *The Lancet* 1999; 353: 1959-64
Possible mechanisms underlying neuropathic syndromes

• CRPS
  – Sympathetic sprouting
  – Microglial activation

• Phantom limb pain
  – Deafferentation
  – Ectopic discharge

• PHN
  – Irritable nociceptors
  – Deafferentation
  – α2δ1 subunit Ca channel
  – TRPV1 receptor

Woolf CJ et al., *The Lancet* 1999; 353: 1959-64
Can we tailor pharmacotherapy based on the neuropathic pain phenotypes (symptoms and syndromes)?
Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

- Standardized quantitative sensory testing was used in 902 (test cohort) and 233 (validation cohort) patients with peripheral neuropathic pain of different etiologies to:
  - subgroup the patients on the basis of characteristic sensory profiles
  - establish a sensory profile-based organizing principle of neuropathic pain
  - replicate the results in a second independent cohort of more than 200 patients

- Three large multinational consortia collected phenotypic data of patients with peripheral neuropathic pain (test cohort): the German Research Network on Neuropathic Pain (DFNS), the EUROPAIN, and the NEUROPAIN collaboration.

Baron R et al., *Pain* 2017 Feb; 158:261-272
Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

• Patients with peripheral neuropathic pain of several etiologies (polyneuropathy [PNP], peripheral nerve injury [PNI], postherpetic neuralgia [PHN], and radiculopathy [RAD]) were included.

• Cluster 1 (sensory loss, 42%) showed a loss of small and large fiber function in combination with paradoxical heat sensations.

• Cluster 2 (thermal hyperalgesia, 33%) was characterized by preserved sensory functions in combination with heat and cold hyperalgesia and mild dynamic mechanical allodynia.

• Cluster 3 (mechanical hyperalgesia, 24%) was characterized by a loss of small fiber function in combination with pinprick hyperalgesia and dynamic mechanical allodynia.

Baron R et al., Pain 2017; 158:261-272
Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

Cluster characteristics, hypotheses on underlying pathophysiology, and rational pharmaceutical treatment.

<table>
<thead>
<tr>
<th></th>
<th>Sensory loss</th>
<th>Thermal hyperalgesia</th>
<th>Mechanical hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original data set, n (%)</td>
<td>381 (42)</td>
<td>302 (33)</td>
<td>219 (24)</td>
</tr>
<tr>
<td>Validation data set, n (%)</td>
<td>124 (53)</td>
<td>77 (33)</td>
<td>32 (14)</td>
</tr>
</tbody>
</table>

Sensory profile

- Sensory loss: Touch, thermal, pain
- Hyperalgesia: None
- DMA: Little
- PHS: Much

Pathophysiology

- Sensory loss: Small and large fibres
- Hyperalgesia: Mostly peripheral sensitization
- Ongoing pain: Spontaneous activity in surviving nociceptors
- DMA: Mostly small fibres
- PHS: Mostly central sensitization
- (Ectopic?) activity in nociceptors

DMA, dynamical mechanical allodynia
PHS, paradoxical heat sensation

Baron R et al., *Pain* 2017; 158:261-272
PHARMACOLOGIC THERAPIES FOR NEUROPATHIC PAIN
Pharmacological Treatment of Neuropathic Pain

- Symptomatic relief and prevention of neurologic sequelae

- Challenging: with only some 40-60% of patients achieving partial relief:
  - Complex pathophysiology
  - The precise mechanisms are unknown
  - Multiple mechanisms may coexist in one patient

- Empirical and Off-label

- Titration and monitoring of treatment

- Treat the underlying condition that may be causing the pain

Kalso E et al., Drugs for Neuropathic pain. *BMJ* 2013. 19;347:f7339
FDA-approved pharmacotherapy for Neuropathic Pain

- Lidocaine (patch 5%)
  - PHN
- Capsaicin (patch 8%)
  - PHN
- Gabapentin
  - PHN
- Pregabalin
  - PHN
  - PDN
  - Spinal cord injury
- Duloxetine & Tapentadol
  - PDN
- Carbamazepine
  - Trigeminal neuralgia
- Ziconotide
  - Severe chronic pain that is intolerant of or refractory to other treatment
<table>
<thead>
<tr>
<th>Group</th>
<th>First-Line Treatment</th>
<th>Second-Line Treatment</th>
<th>Third-Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Pain Society, CPS²⁹</td>
<td>TCAs, Anticonvulsants</td>
<td>SNRIs, Topical lidocaine</td>
<td>Tramadol, Opioids</td>
</tr>
<tr>
<td>EFNS²⁷</td>
<td>SNRI, Pregabalin, TCAs</td>
<td>Tramadol, Opioids</td>
<td></td>
</tr>
<tr>
<td>IASP NeuroPSIG³¹</td>
<td>SNRIs, TCAs, Gabapentin, Pregabalin</td>
<td>Tramadol, Opioids</td>
<td>Antidepressants (bupropion, citalopram, paroxetine)</td>
</tr>
<tr>
<td></td>
<td>Topical lidocaine</td>
<td></td>
<td>Anticonvulsants (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topical low-concentration capsaicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dextromethorphan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Memantine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mexiletine</td>
</tr>
</tbody>
</table>

SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressants.

Jongen JL et al., *Pain Practice* 2014 (14); 3: 283–295
Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

New recommendations from NeuPSIG

<table>
<thead>
<tr>
<th></th>
<th>Comparisons*</th>
<th>Participants†</th>
<th>Active pain relief</th>
<th>Placebo</th>
<th>Number needed to treat (95% CI)</th>
<th>Susceptibility to bias‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic</td>
<td>15</td>
<td>948</td>
<td>217/473</td>
<td>85/475</td>
<td>3.6 (3.0–4.4)</td>
<td>1973</td>
</tr>
<tr>
<td>antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin-</td>
<td>10</td>
<td>2541</td>
<td>676/1559</td>
<td>278/982</td>
<td>6.4 (5.2–8.4)</td>
<td>1826</td>
</tr>
<tr>
<td>noradrenaline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reuptake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25</td>
<td>5940</td>
<td>1359/3530</td>
<td>578/2410</td>
<td>7.7 (6.5–9.4)</td>
<td>2534</td>
</tr>
<tr>
<td>Gabapentin§</td>
<td>14</td>
<td>3503</td>
<td>719/2073</td>
<td>291/1430</td>
<td>7.2 (5.9–9.1)</td>
<td>1879</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6</td>
<td>741</td>
<td>176/380</td>
<td>96/361</td>
<td>4.7 (3.6–6.7)</td>
<td>982</td>
</tr>
<tr>
<td>Strong opioids</td>
<td>7</td>
<td>838</td>
<td>211/426</td>
<td>108/412</td>
<td>4.3 (3.4–5.8)</td>
<td>1326</td>
</tr>
<tr>
<td>Capsaicin 8%</td>
<td>6</td>
<td>2073</td>
<td>466/1299</td>
<td>212/774</td>
<td>10.6 (7.4–18.8)</td>
<td>70¶</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>4</td>
<td>137</td>
<td>42/70</td>
<td>4/67</td>
<td>1.9 (1.5–2.4)</td>
<td>678</td>
</tr>
</tbody>
</table>

Finnerup NB et al., *Lancet Neurol* 2015; 162-73
New recommendations from NeuPSIG

<table>
<thead>
<tr>
<th></th>
<th>Total daily dose and dose regimen</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong recommendations for use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gapabentin</td>
<td>1200–3600 mg, in three divided doses</td>
<td>First line</td>
</tr>
<tr>
<td>Gabapentin extended release or enacarbil</td>
<td>1200–3600 mg, in two divided doses</td>
<td>First line</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300–600 mg, in two divided doses</td>
<td>First line</td>
</tr>
<tr>
<td>Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*</td>
<td>60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)</td>
<td>First line</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>25–150 mg, once a day or in two divided doses</td>
<td>First line†</td>
</tr>
<tr>
<td><strong>Weak recommendations for use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin 8% patches</td>
<td>One to four patches to the painful area for 30-60 min every 3 months</td>
<td>Second line (peripheral neuropathic pain)‡</td>
</tr>
<tr>
<td>Lidocaine patches</td>
<td>One to three patches to the region of pain once a day for up to 12 h</td>
<td>Second line (peripheral neuropathic pain)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>200–400 mg, in two (tramadol extended release) or three divided doses</td>
<td>Second line</td>
</tr>
<tr>
<td>Botulinum toxin A (subcutaneously)</td>
<td>50–200 units to the painful area every 3 months</td>
<td>Third line; specialist use (peripheral neuropathic pain)</td>
</tr>
<tr>
<td>Strong opioids</td>
<td>Individual titration</td>
<td>Third line§</td>
</tr>
</tbody>
</table>

Finnerup NB et al., *Lancet Neurol* 2015; 162-73
Changes in the recommendations of NeuPSIG

- **No longer propose lidocaine patches as first line** because of weak quality of evidence. However, because of the excellent safety profile, high values and preferences, and initial positive short-term studies, we propose lidocaine as a second-line treatment for peripheral neuropathic pain.

- **Strong opioids are now recommended as third line**, contrasting with several previous recommendations in which they were generally thought of as first or second line. This stems mainly from the consideration of potential risk of abuse, particularly with high doses, and concerns about a recent increase in prescription-opioid-associated overdose mortality, diversion, misuse, and other opioid-related morbidity particularly in the USA, Canada, and the UK.

- **High-concentration capsaicin patches** and **cannabinoids** (so far positive evidence for *Multiple Sclerosis* only) are considered for the first time in therapeutic recommendations for neuropathic pain.

  Finnerup NB et al., *Lancet Neurol* 2015; 162-73
Membrane stabilizers

• Calcium channel blockers
  — **Gabapentin** (Neurontin) and **Pregabalin** (Lyrica) are preferred first-line medications for DPN
  — Ziconotide

• Sodium channel blockers
  — **Topiramate**: weight loss
  — **Carbamazepine** (Tegretol) and **Oxcarbazepine** (Trileptal) are especially effective in TN
  — **Lamotrigine**: CPSP, TN (carbamazepine-resistant TN), SCI, MS

• Start low, go slow
• Watch for side effects, monitor serum levels and dose adjustment
Antidepressants

• Activation of descending norepinephrinergic and serotonergic pathways to the spinal cord limit pain signals ascending to the brain.

• Antidepressants relieve neuropathic pain in non-depressed persons.

• Tricyclic antidepressants
  – Analgesic effects separate from anti-depressant effects
  – Amitriptyline: most studied, but most side effects
  – Nortriptyline & Desipramine: better tolerated, less studied

• SSRIs: little evidence of analgesic effect.

• SNRI’s
  – inhibit both norepinephrine and serotonin reuptake
  – efficacy in neuropathic pain syndromes or pain associated with depression (Duloxetine [Cymbalta®], Venlafaxine [Effexor®], Milnacipran [Savella®])
Mechanism-based pharmacotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>NEURONAL PROCESSES, MECHANISMS</th>
<th>TARGETS</th>
<th>OPTIMAL COMPOUNDS</th>
<th>AVAILABLE COMPOUNDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous pain (shooting)</td>
<td>Peripheral nociceptor hyperexcitability: Ectopic impulse generation, oscillations in dorsal root ganglion</td>
<td>Sodium channels</td>
<td>Selective sodium-channel blockers</td>
<td>Lidocaine, carbamazepine, oxcarbazepine, lamotrigine, TCA</td>
</tr>
<tr>
<td>Spontaneous pain (ongoing)</td>
<td>Peripheral nociceptor sensitization: <em>Inflammation within nerves</em> Cytokine release</td>
<td>Cytokines</td>
<td>Cytokine antagonists Cyclooxygenase blockers</td>
<td>TNF-α antagonists NSAIDS?</td>
</tr>
<tr>
<td>Heat allodynia</td>
<td><em>Reduced activation threshold to:</em> Heat</td>
<td>TRPV1 receptor</td>
<td>TRPV1-receptor antagonists</td>
<td>Capsaicin cream</td>
</tr>
<tr>
<td>Cold allodynia</td>
<td></td>
<td>TRPM8 receptor</td>
<td>TRPM8-receptor antagonists</td>
<td>Menthol?</td>
</tr>
<tr>
<td>Static mechanical allodynia</td>
<td>Mechanical stimuli</td>
<td>ASIC receptor?</td>
<td>ASIC-receptor antagonists</td>
<td>?</td>
</tr>
<tr>
<td>SMP</td>
<td>Noradrenaline</td>
<td>α receptor</td>
<td>α-receptor antagonists</td>
<td>Phentolamine, sympathetic block, TCA</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
<td>Histamine H1 receptor</td>
<td>H1-receptor antagonists</td>
<td>TCA</td>
</tr>
</tbody>
</table>

# Mechanism-based pharmacotherapy for neuropathic pain

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>NEURONAL PROCESSES, MECHANISMS</th>
<th>TARGETS</th>
<th>OPTIMAL COMPOUNDS</th>
<th>AVAILABLE COMPOUNDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic mechanical allodynia</td>
<td>Central dorsal horn hyperexcitability</td>
<td>Presynaptic: μ-receptors Calcium channels (α2-δ)</td>
<td>μ-receptor agonists Calcium-channel blocker, α2-δ ligands</td>
<td>Opioids Gabapentin, pregabalin</td>
</tr>
<tr>
<td>Punctate mechanical hyperalgesia</td>
<td>Central sensitization on spinal level Ongoing C-Input induces increased synaptic transmission Amplification of C-fiber input Gating of Aβ-fiber input (mechanical dynamic hyperalgesia) Gating of Aδ-fiber input (mechanical punctate hyperalgesia) Intraspinal inhibitory interneurons (functional, degeneration) GABA-ergic Opioidergic Changes in supraspinal descending modulation Inhibitory control (noradrenaline, 5-HT) ↓ Facilitatory control ↑</td>
<td>Postsynaptic: NMDA receptors NK1 receptors Sodium channels Intracellular cascades</td>
<td>NMDA-receptor antagonists NK1-receptor antagonists Selective sodium-channel blocker MAPK mediators</td>
<td>Ketamine, dextromethorphan? Carbamazepine?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; receptors μ-receptors</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; agonists μ-receptor agonists</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α2 receptors 5-HT receptors</td>
<td>α2-receptor agonists NA/5-HT-reuptake-blocker</td>
</tr>
</tbody>
</table>
Mechanism-based pharmacotherapy for PHN

• Spontaneous pain
  – Activation of A2δ1 Ca channel, Na channel
    – Gabapentin or pregabalin, lidocaine cream/patch
  – Reduced descending inhibition
    – TCAs, SNRIs

• Without allodynia: No sensory loss
  – Nonsignificant pain relief by topical lidocaine

• With allodynia: Irritable nociceptors
  – Statistically significant pain reduction with topical lidocaine

• Thermal hyperalgesia
  – “Irritable Na channel”: Na-channel anticonvulsant eg oxcarbazepine
  – Up-regulation of TRPV1 receptors: Capsaicin cream

Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles

Cluster characteristics, hypotheses on underlying pathophysiology, and rational pharmaceutical treatment.

<table>
<thead>
<tr>
<th></th>
<th>Sensory loss</th>
<th>Thermal hyperalgesia</th>
<th>Mechanical hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original data set, n (%)</td>
<td>381 (42)</td>
<td>302 (33)</td>
<td>219 (24)</td>
</tr>
<tr>
<td>Validation data set, n (%)</td>
<td>124 (53)</td>
<td>77 (33)</td>
<td>32 (14)</td>
</tr>
</tbody>
</table>

Pathophysiology

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Sensory loss</th>
<th>Thermal hyperalgesia</th>
<th>Mechanical hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory loss</td>
<td>Small and large fibres</td>
<td>—</td>
<td>Mostly small fibres</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>—</td>
<td>Mostly peripheral sensitization</td>
<td>Mostly central sensitization</td>
</tr>
<tr>
<td>Ongoing pain</td>
<td>Ectopic activity in damaged nociceptors or in CNS neurons</td>
<td>Spontaneous activity in surviving nociceptors</td>
<td>(Ectopic?) activity in nociceptors</td>
</tr>
</tbody>
</table>

Predicted efficacy

<table>
<thead>
<tr>
<th>Predicted efficacy</th>
<th>NSADS</th>
<th>Botox</th>
<th>Topical capsaicin</th>
<th>NMDA-antagonist</th>
<th>Antidepressant</th>
<th>Gabapentinoid</th>
<th>Na-channel blocker</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

DMA, dynamical mechanical allodynia
PHS, paradoxical heat sensation

Baron R et al., *Pain* 2017; 158:261-272
A Systematic Review of Treatment of Painful Diabetic Neuropathy by Pain Phenotype versus Treatment Based on Medical Comorbidities

• Out of 45 identified papers, 7 were thoroughly reviewed.
• Four RCTs stratified according to pain phenotype
• Three main results:
  – (1) paroxysmal pain had a better response to pregabalin;
  – (2) the preservation of thermal sensation or nociception anticipated a positive response to the topical treatment of pain;
  – (3) after a failure to duloxetine (60 mg/day), the patients with evoked pain or severe deep pain had a better response to association of duloxetine/pregabalin while those with paresthesia/dysesthesia benefited from duloxetine monotherapy (120 mg/day).

Clemente Rolim L et al., *Front Neurol.* 2017 Jun;8:285
Drug combination for neuropathic pain

Table 5. Efficacy of Drug Combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Condition</th>
<th>Nature of Study</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilron et al.</td>
<td>Gabapentin + morphine</td>
<td>PHN, DPN</td>
<td>P, R, C</td>
<td>Positive</td>
</tr>
<tr>
<td>Gilron et al.</td>
<td>Gabapentin + nortriptyline</td>
<td>PHN, DPN</td>
<td>P, R, C</td>
<td>Positive</td>
</tr>
<tr>
<td>Baron et al.</td>
<td>Gabapentin + lidocaine plaster</td>
<td>PHN, DPN</td>
<td>P, R, C</td>
<td>Positive</td>
</tr>
<tr>
<td>Hanna et al.</td>
<td>Gabapentin + oxycodone</td>
<td>DPN</td>
<td>P, R, C</td>
<td>Positive</td>
</tr>
<tr>
<td>Zin et al.</td>
<td>Oxycodone + pregabalin</td>
<td>PHN, DPN</td>
<td>P, R, C</td>
<td>No difference</td>
</tr>
<tr>
<td>Khoromi et al.</td>
<td>Morphine + nortriptyline</td>
<td>Lumbosacral radiculitis</td>
<td>P, R, C</td>
<td>No difference</td>
</tr>
<tr>
<td>Mercadante et al.</td>
<td>Morphine + amitriptyline</td>
<td>Neuropathic cancer pain</td>
<td>P, R, C, Crossover</td>
<td>No difference</td>
</tr>
</tbody>
</table>

C, controlled; DPN, diabetic painful neuropathy; P, prospective; PHN, postherpetic neuralgia; R, randomized.

Jongen JL et al., *Pain Practice* 2014 (14); 3: 283–295
Morphine, Gabapentin, or Their Combination for Neuropathic Pain

• Randomized, double-blind, active placebo (lorazepam)-controlled in patients with PDN and PHN

• The primary outcome: mean daily pain intensity in patients receiving a maximal tolerated dose

• Secondary outcomes included pain (rated according to the Short-Form McGill Pain Questionnaire), adverse effects, maximal tolerated doses, mood, and quality of life.

Gilron I et al., NEJM 2005; 352:1324-1334
The combination treatment with morphine and gabapentin resulted in a greater reduction in pain than did gabapentin alone, morphine alone, or placebo.

The combination therapy also had beneficial effects on pain-related interference with daily activities, mood, and health-related quality of life.

The combination therapy resulted in a greater frequency of constipation than gabapentin alone did and a greater frequency of dry mouth than morphine alone did.

Gilron I et al., NEJM 2005; 352:1324-1334
Gabapentin Plus Opioids: a Deadly Combination?

• A matched case–control study among people treated with opioid painkillers in Ontario, the most populous province of Canada.
• To determine concomitant gabapentin exposure among 1,256 individuals (cases) who died of an opioid-related cause and 4,619 matched controls.
• They found that concomitant gabapentin and opioid exposure was associated with a 49% higher risk of dying from an opioid overdose.
• Clinicians should take great caution when combining gabapentin and opioids.
• Patients treated with opioids and gabapentin should be closely monitored, and may need to have their doses adjusted to avoid potential drug overdose.

Gomes T et al., PLOS Medicine 2017 Oct
Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial

Ian Gilron, Joan M Bailey, Dongsheng Tu, Ronald R Holden, Alan C Jackson, Robyn L Houlden

- Double-blind, double-dummy, crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia
- Gabapentin 600mg TID, nortriptyline 50mg QHS
- Mean daily pain scale was 5.4 (95% CI 5.0 to 5.8) at baseline, and at maximum tolerated dose, pain was 3.2 (2.5 to 3.8) for gabapentin, 2.9 (2.4 to 3.4) for nortriptyline, and 2.3 (1.8 to 2.8) for combination treatment.
- Pain with combination treatment was significantly lower than with gabapentin (–0.9, 95% CI –1.4 to –0.3, p=0.001) or nortriptyline alone (–0.6, 95% CI –1.1 to –0.1, p=0.02).
- No serious adverse events were recorded for any patients during the trial.
- Supported by Canadian Institute of Health (not pharmaceutical company), two inexpensive generic medications

Gilron I et al., Lancet 2009; 374:1252-61
Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial

Ian Gilron, Luis E. Chaparro, Dongsheng Tu, Ronald R. Holden, Roumen Milev, Tanveer Towheed, Deborah DuMerton-Shore, Sarah Walker

• Single-center, randomized controlled trial
• 41 patients with fibromyalgia (age range, 18-70 years)
• Patients were randomly assigned to one of 24 possible medication sequences over four six-week periods. The target daily dosage ceiling was 450 mg of pregabalin and 120 mg of duloxetine
• The primary outcome measure was “average pain intensity over the past 24 hours”. The secondary outcome measure was global pain relief

Pain 2016;157:1532-1540.
Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial

Ian Gilron\textsuperscript{a,b,i,*}, Luis E. Chaparro\textsuperscript{c}, Dongsheng Tu\textsuperscript{d,e}, Ronald R. Holden\textsuperscript{f}, Roumen Miley\textsuperscript{g}, Tanveer Towheed\textsuperscript{h}, Deborah DuMerton-Shore\textsuperscript{i}, Sarah Walker\textsuperscript{j}

Pain 2016;157:1532-1540.
Pain 2016;157:1532-1540.
Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial

Ian Gilron\textsuperscript{a,b,i,*}, Luis E. Chaparro\textsuperscript{c}, Dongsheng Tu\textsuperscript{d,e}, Ronald R. Holden\textsuperscript{f}, Roumen Milev\textsuperscript{g}, Tanveer Towheed\textsuperscript{h}, Deborah DuMerton-Shore\textsuperscript{i}, Sarah Walker\textsuperscript{j}

- The \textbf{average pain rating} (mean ± SEM) at ceiling dose was 3.7±0.3 for combination therapy, compared with 5.1±0.3 for placebo ($P<0.001$) and 5.0±0.3 for pregabalin alone ($P<0.001$). The average pain rating for combination therapy was also lower than for duloxetine alone; however, this finding was not statistically significant ($P=0.09$).

- Moreover, in terms of \textbf{global pain relief}, a secondary outcome measure, 67.7% of patients reported moderate or greater pain relief from combination therapy, compared with 38.5% for pregabalin ($P=0.02$) and 41.7% for duloxetine ($P=0.03$).

Pain 2016;157:1532-1540.
Case practice - PDN

63 year old male with type 2 diabetes diagnosed about five years ago that is relatively well controlled with insulin.

He has early signs of retinopathy, with normal kidney function and electrocardiogram. Lipid values are normal with diet and atorvastatin 20 mg/day.

He developed autonomic and peripheral neuropathy a few months ago, and now experiences postural hypotension and burning pain and clumsiness in his feet. His pain makes concentration and falling asleep difficult. He asks his general practitioner for painkillers to help him continue working.

Kalso E et al., Drugs for Neuropathic pain. BMJ 2013. 19;347:f7339.
Case practice – selection of drugs

• The patient’s general practitioner decided to avoid TCAs as the patient had postural hypotension.

• *Gabapentin* TID was prescribed as he had been having difficulty sleeping. This produced good pain relief and improved sleep, but daytime sedation and dizziness were problematic.

• Gabapentin was changed to *pregabalin* twice daily, which also caused daytime dizziness. This dizziness resolved with a lower morning dose, but daytime pain increased.

• *Duloxetine* was added. Initial nausea with duloxetine disappeared in a few days, and the dose was increased.

• On both *pregabalin* and *duloxetine*, the patient described his pain intensity as mild and he continues to work.

Kalso E et al., Drugs for Neuropathic pain. *BMJ* 2013. 19;347:f7339.
I do not feel better, so clearly the medication isn’t working.
Go back to the mechanisms!

Neuropathic pain is sympathetically maintained?

- Lumbar sympathetic block
- Stellate ganglion block
- $\alpha_1$ antagonists
  - Phentolamine
  - Terazosin: 1 mg qHS, can titrate to 3-5 mg qHS as tolerated
- Case reports

Smith H et al., Curr Opin Anaesthesiol. 2001 Oct; 14:513-8
Continue review the mechanisms: Central sensitization

- NMDA receptor activation
- Loss of GABA inhibition
- Microglia activation

NMDA receptor antagonists

• Ketamine
  – CRPS, cancer related pain

• Dextromethorphan
  – DPN (Shaibani et al., *Pain Med* 2012 Feb; 13(2):243-54)
  – Human Experimental Model of Hyperalgesia, only after NMDA is activated (Martin et al., *Anesthesiology* 2019 May)

• Memantine
  – Phantom limb pain (Buvanendran et al., *Anesth Analg* 2008;107(4):1093-4)
  – SNL pain (Morel et al., *Behavioural Pharmacology*, 2013; 721:382-390)

• Methadone

• Magnesium

• Selective NR2B antagonist
  – Ifenprodil and Traxoprodil
IV Ketamine infusion in CRPS

• Clinical evidence demonstrated efficacy


• Widely used however no consensus protocol among providers

• Survey study, Consensus meeting, and Reference protocol


• Validation of the consensus protocol and Comprehensive outcome measures are underway
Microglial modulators

- **Low dose naltrexone (LDN)**
  - Off-label, case reports
  - Effective in Fibromyalgia, DPN, CRPS, Crohn’s
    - those with autoimmune and/or neuroinflammatory components?
  - Dosages range from 1.5 mg to 4.5 mg once daily
  - Titration: 1, 2, and 4 mg qHS for 2 weeks each

Reinstitution of GABA inhibition

- Intrathecal baclofen
  - FDA approved for spasticity
  - Case series
  - Off-label used for neuropathic pain secondary to
    - Spinal Cord Injury
    - CRPS
    - Amputation, Postlaminectomy, GSW, etc

Zuniga RE et al., Intrathecal baclofen is analgesic in patients with chronic pain. *Anesthesiology.* 2000 Mar;92(3):876-80
Summary

• Mechanisms underlying neuropathic pain
  – **Peripheral sensitization**: NaV 1.7/1.8, NGF, TRPV1R, α-adrenal receptor, nAChR
  – **Central sensitization**: NMDA receptors activation, loss of GABA inhibition, Microglia activation
  – Functional deafferentation
  – Genetics

• Mechanism-based pharmacological therapies
  – Membrane stabilizers (Ca, Na channel blockers), TCAs, SNRIs
  – Capsaicin to deplete TRPV receptors
  – α1 antagonists for sympathetic-maintained pain
  – NMDA receptor inhibitor: ketamine
  – Microglial modulator: LDN
  – Reinstitution of GABA inhibition: intrathecal baclofen
  – Novel targets: Nav1.7/1.8, HCN2, CB2, NGF, AT2, nAChR
  – Because of the limited efficacy of these drugs, off-label prescribing is widespread. Many times, a combination of drugs targeting different mechanisms should be considered.
Remember, pharmacotherapy is only a small portion of neuropathic pain management!
Bibliographies

- Raj’s Practical Management of Pain, 5th Ed 2013
- Rosenquist E. Definition and pathogenesis of chronic pain. Up to date.
- Lana B et al., Differential upregulation in DRG neurons of an α2δ-1 splice variant with a lower affinity for gabapentin after peripheral sensory nerve injury. Pain 2014 Mar;155(3):522-33
- Edward C. et al., HCN2 Ion Channels Play a Central Role in Inflammatory and Neuropathic Pain. Science, September 9, 2011, 1462-1466
- Kalso E et al., Drugs for Neuropathic Pain. BMJ 2013:347:f7339
- Karst et al., Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain. JAMA 2003; 290:1757-1762
Every Pain Deserves World Class Care.