PAIN

Focus on

Pain in Clinical Practice

dr. Debby Amelia, SpS
What is pain?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain (IASP) 2011
What Is Pain?

- Sensory vs emotional
- Acute vs chronic pain
- Malignant vs non-malignant pain
- Nociceptive vs neuropathic pain
- Stimulus-independent vs stimulus-evoked pain
- Hyperalgesia vs allodynia
- Mild vs moderate vs severe pain
- Sympathetically mediated pain (SMP)
Multiple Types of Pain

A. Nociceptive

Noxious Peripheral Stimuli

Examples

- Strains and sprains
- Bone fractures
- Postoperative

Inflammatory

Inflammation

- Osteoarthritis
- Rheumatoid arthritis
- Tendonitis

B. Neuropathic

Multiple Mechanisms

- Diabetic peripheral neuropathy
- Post-herpetic neuralgia
- HIV-related polyneuropathy

C. Psikogenic

Abnormal Central Processing

No Known Tissue or Nerve Damage

- Fibromyalgia
- Irritable bowel syndrome

Patients may experience multiple pain states simultaneously

NOCICEPTION
PAIN
SUFFERING
PAIN BEHAVIOUR

Phenomenon of Pain

(Stanton-Hicks M, Boas R, 1982)
Pain Is the 5th Vital Sign

Respiration | Pulse | Blood pressure | Temperature

Pain

Pain Classification

Mechanism of Pain

- **Transduction**: Peripheral nociceptors
- **Transmission**: Dorsal root ganglion
- **Modulation**: Descending modulation

**Spinothalamic tract**

The Pain Continuum

**Time to resolution**

**Insult**

**Acute pain**

*Normal, time-limited response to ‘noxious’ experience (less than 3 months)*

- Usually obvious tissue damage
- Serves a protective function
- Pain resolves upon healing

**Chronic pain**

*Pain that has persisted beyond normal tissue healing time (usually more than 3 months)*

- Usually has no protective function
- Degrades health and function

Acute pain may become chronic

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Long-Term Consequences of Acute Pain
Potential for Progression to Chronic Pain

- Surgery or injury causes inflammation
- Peripheral Nociceptive Fibers
- Peripheral Nociceptive Fibers
- CNS Neuroplasticity
  - Hyperactivity

ACUTE PAIN

- Long-Term Consequences of Acute Pain
- Potential for Progression to Chronic Pain

Time-based classification of pain

- **Acute**: short-term; usually due to nociception (tissue damage); resolves with healing.

- In back pain, Acute = < 4 wks
  Sub-acute = 4-12 weeks
  Chronic = > 12 weeks

- **Chronic pain**: pain lasting > 3-6 months

- **Persisting pain** (NHMRC: acute pain guidelines)
Prevalence of Acute Pain

• **Lifetime** prevalence in general population:
  – Approaches **100%** for acute pain leading to use of analgesics\(^1\)

• **Emergency room** patients:
  – Pain accounts for **>2/3** of emergency room visits\(^2\)

• **Hospitalized** patients:
  – **>50%** report pain\(^3\)

Multiple pain mechanisms may coexist (mixed pain)

Nociceptive pain
- Somatic
- Visceral

Neuropathic pain
- Peripheral
- Central

Central sensitization/dysfunctional pain

Pathophysiological Classification of Pain

Ungkapan Nyeri

- Aching = nyeri
- Stabbing = tertusuk / tikam
- Tender = nyeri tekan
- Tiring = nyeri melelahkan
- Numb = baal
- Dull = nyeri tumpul
- Crampy = nyeri kram
- Throbbing = nyeri seperti tercekik
- Gnawing = nyeri seperti digigit
- Burning = rasa terbakar

- Shooting = rasa menyentak
- Sharp = nyeri tajam
- Exhausting = nyeri melelahkan
- Nagging = perih
- Unbearable = tidak tertahankan
- Squeezing = seperti diremas
- Pressure = seperti ditekan
- Penetrating = rasa tertembus
- Miserable = menyusahkan
- Radiating = menjalar
- Deep = nyeri dalam
Terminologi Seputar Nyeri

• **Allodynia**
  – Nyeri yang disebabkan oleh stimulus secara normal tidak menimbulkan nyeri

• **Hyperalgesia**
  – Respon yang berlebihan terhadap stimulus yang secara normal menimbulkan nyeri.

• **Hyperpathia**
  – Sindroma dengan nyeri bercirikan reaksi nyeri abnormal terhadap stimulus, khususnya stimulus berulang, seperti peninggian batas ambang.
Terminologi Seputar Nyeri

• Hypoalgesia
  – berkurangnya respon nyeri terhadap stimulus yang dalam keadaan normal menimbulkan nyeri

• Paresthesia
  – Sensasi abnormal, yang tidak menyenangkan baik spontan ataupun dengan pencetus.

• Neuralgia
  – Nyeri pada daerah distribusi saraf.
Terminologi Seputar Nyeri

• **Analgesia**
  – Hilangnya respon nyeri terhadap stimulus yang dalam keadaan normal menimbulkan nyeri.

• **Anesthesia dolorosa**
  – Nyeri pada area atau regio yang semestinya bersifat anestetik.

• **Causalgia**
  – Sindroma yang timbul pada lesi saraf paska trauma yang ditandai nyeri seperti terbakar, alodinia, hiperpatia yang menetap, seringkali bercampur dengan disfungsi vasomotor serta sudomotor dan kemudian diikuti oleh gangguan trofik.
NEUROTRANSMITTER PADA MODULASI NYERI

<table>
<thead>
<tr>
<th>Neurotransmiter</th>
<th>Reseptor</th>
<th>Efek nosisepsi</th>
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<tbody>
<tr>
<td>NE</td>
<td>α2</td>
<td>inhibisi</td>
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<tr>
<td>5-HT</td>
<td>5HT1,5HT2,5HT3</td>
<td>inhibisi</td>
</tr>
<tr>
<td>GABA</td>
<td>GABA-A,GABA-B</td>
<td>inhibisi</td>
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<td>Glisin</td>
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<td>inhibisi</td>
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<td>Glutamat</td>
<td>NMDA,AMPA,kainat,mGluR</td>
<td>eksitasi</td>
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<tr>
<td>Aspartat</td>
<td>NMDA,AMPA,kainat,mGluR</td>
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<td>NO</td>
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<td>Asetilkolin</td>
<td>muskarinin</td>
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<td>Enkefalin</td>
<td>δOP1,κOP2, μOP3</td>
<td>inhibisi</td>
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<td>SP</td>
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<td>CCK</td>
<td>CCK-B</td>
<td>antagonis*</td>
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<td>Galanin</td>
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<td>inhibisi</td>
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<td>Somatostatin</td>
<td>sst</td>
<td>inhibisi</td>
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<tr>
<td>Neuropeptide Y</td>
<td>Y1, Y2</td>
<td>inhibisi</td>
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<tr>
<td>Neurotensin</td>
<td>NTS 1</td>
<td>inhibisi</td>
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<tr>
<td>Bradikinin</td>
<td>B2 (B1)</td>
<td>eksitasi</td>
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<td>Adenosin</td>
<td>A 1</td>
<td>inhibisi</td>
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<td>Purin</td>
<td>P2X3</td>
<td>eksitasi</td>
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<td>Sitokin</td>
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<td>eksitasi</td>
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<tr>
<td>Kapsaisin</td>
<td>VR1</td>
<td>eksitasi</td>
</tr>
<tr>
<td>Kannabinoid</td>
<td>CB1</td>
<td>inhibisi</td>
</tr>
</tbody>
</table>

* fungsional antagonis opioid-induced analgesia
Pain Rating Scales

10 Pain Intensity Scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td><strong>Moderate</strong></td>
<td><strong>Severe</strong></td>
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Pain threshold

Pain tolerance
Sites of origin of pain within the nociceptive pathway
What is nociceptive pain?

**Definition**
- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Can be somatic or visceral

**Pain Quality**
- Usually aching or throbbing
- Usually time-limited (resolves when damaged tissue heals)
- Usually well localized if somatic
- May be referred if visceral
- Can become chronic

## PERBEDAAN SECARA UMUM NYERI NOSISEPTIK DAN NYERI NEUROPATHIK:

<table>
<thead>
<tr>
<th>NYERI NOSISEPTIK</th>
<th>NYERI NEUROPATHIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Terlokalisasi pada tempat cedera.</td>
<td>- Nyeri di bagian distal dari lesi atau disfungsi saraf.</td>
</tr>
<tr>
<td>- Sensasi sesuai stimulus, misalnya jika terbakar akan terasa panas, jika tertusuk pisau maka lesi seperti ditikam dan lain-lain.</td>
<td>- Sensasi tidak selalu sesuai stimulus, rasa panas, berdenyut, ngilu, kaku.</td>
</tr>
<tr>
<td>- Akut, mempunyai batas waktu. Nyeri menghilang setelah cedera sembuh.</td>
<td>- Kronis, persisten setelah cedera menyembuh.</td>
</tr>
<tr>
<td>- Memiliki fungsi protektif</td>
<td>- Tidak memiliki fungsi protektif</td>
</tr>
</tbody>
</table>
Nociceptive Pain

**Somatic**
- Musculoskeletal injury
- Post-operative pain
- Burn pain

**Visceral**
- Ischemic, e.g., myocardial infarction
- Abdominal colic
- Infection, e.g., pharyngitis
- Dysmenorrhea

# Somatic vs. Visceral Pain

<table>
<thead>
<tr>
<th><strong>Somatic</strong></th>
<th><strong>Visceral</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nociceptors are involved</td>
<td>• Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation</td>
</tr>
<tr>
<td>• Often well localized</td>
<td>• Pain is usually referred, poorly localized, vague and diffuse</td>
</tr>
<tr>
<td>• Usually described as throbbing or aching</td>
<td>• May be associated with autonomic symptoms (e.g., pallor, sweating, nausea, blood pressure and heart rate changes)</td>
</tr>
<tr>
<td>• Can be superficial (skin, muscle) or deep (joints, tendons, bones)</td>
<td></td>
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</tbody>
</table>

Referred Pain

Patofisiologi Nyeri

<table>
<thead>
<tr>
<th>Nyeri</th>
<th>Transduksi</th>
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<tbody>
<tr>
<td></td>
<td>Transmisi</td>
</tr>
<tr>
<td></td>
<td>Persepsi</td>
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<tr>
<td></td>
<td>Modulasi</td>
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</table>
PAIN – SERIES OF EVENTS

PERCEPTION

MODULATION

TRANSMISSION

TRANSDUCTION
Nociception: Neural Process of Encoding Noxious Stimuli

Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Pain Modulation

- Pain is modulated via **ascending nociceptive** and **descending inhibitory/facilitatory** spinal tracts

<table>
<thead>
<tr>
<th>Ascending Nociceptive</th>
<th>Descending Inhibitory/facilitatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>C fibers</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Aδ fibers</td>
<td>Norepinephrine</td>
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<td></td>
<td>Dopamine</td>
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</tbody>
</table>

Pain Perception

- Spinal cord transmits pain signals to specific nuclei in the thalamus, and from there to a wide variety of regions in the brain – collectively known as the “pain matrix”

- Pain perception can also be altered without any external stimuli (i.e., through emotion, distraction, placebo, etc.)

Inflammation

Damaged tissue
Inflammatory cells
Tumor cells

Inflammatory chemical mediators

Prostanoids
Cytokines
Growth factors
Kinins
Purines
Amines
Ions

Changed responsiveness of nociceptors (peripheral sensitization)

Nociceptive afferent fiber
Spinal cord

Brain

Changed responsiveness of neurons in CNS (central sensitization)

CNS = central nervous system
What is neuropathic pain?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Pain Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain caused by a lesion or disease of the somatosensory nervous system</td>
<td>• Burning</td>
</tr>
<tr>
<td>• Can be peripheral or central</td>
<td>• Lancinating</td>
</tr>
<tr>
<td></td>
<td>• Electric shock-like</td>
</tr>
<tr>
<td></td>
<td>• Often diffuse</td>
</tr>
<tr>
<td></td>
<td>• Frequently with allodynia and/or hyperalgesia</td>
</tr>
</tbody>
</table>

Recognizing Neuropathic Pain

**Common descriptors**
- Shooting
- Electric shock-like
- Burning
- Tingling
- Numbness

Post-stroke pain

Diabetic peripheral neuropathy

Lumbar radicular pain

Postherpetic neuralgia

Chronic post-surgical pain

Burning, feeling like the feet are on fire

Freezing, like the feet are on ice, although they feel warm to touch

Stabbing, like sharp knives

Lancinating, like electric shocks
Common Descriptors of Neuropathic Pain

- Burning
- Tingling
- Pins and needles
- Electric shock-like
- Numbness

Neuropathic Pain Is Characterized by Changes in Pain Response to Painful Stimuli

Pain intensity vs. Stimulus intensity

**Hyperalgesia** (increased response to a stimulus that is normally painful)

**Allodynia** (pain due to stimulus that does not normally provoke pain)

Mechanisms of Neuropathic Pain

- **Nerve lesion/disease**
- **Loss of inhibitory control**
- **Ectopic discharge**
- **Nociceptive afferent fiber**
- **Descending modulation**
- **Central sensitization**

References:
Mekanisme Nyeri Neuropatik

Mekanisme Perifer:
- a. Aktivitas ektopyik spontan
- b. Sensitisasi nosiseptor
- c. Sprouting kolateral neuron aferen primer
- d. Ephaptic conduction
- e. Perubahan pada ekspresi saluran ion
- f. Sprouting neuron simpatetik ke dalam ganglion radiks dorsalis
- g. Sensitivitas terhadap katekolamin
- h. Rangsangan pada nervi nervorum.

Mekanisme Sentral:
- a. Sensitisasi Sentral
- b. Reorganisasi spinal
- c. Reorganisasi kortikal
- d. Hilangnya kontrol inhibisi
- e. Peningkatan jumlah reseptor
- f. Perubahan pada gene-related C-fos
- g. Lepasan muatan epileptik pada neuron nosiseptif kortikal
**What is central sensitization/dysfunctional pain?**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Examples</th>
<th>Pain Quality</th>
</tr>
</thead>
</table>
| • Amplification of neural signaling within the CNS that elicits pain hypersensitivity | • Fibromyalgia  
• Irritable bowel syndrome  
• Interstitial cystitis  
• Temporomandibular joint pain  
• May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis | • Burning  
• Lancinating  
• Electric shock-like  
• Often diffuse  
• Frequently with allodynia and/or hyperalgesia |

CNS = central nervous system
Nociceptive Vs Neuropathic Pain

**Nociceptive Pain**
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

- Postoperative pain
- Mechanical low back pain
- Sickle cell crisis
- Sports/exercise injuries

**Mixed Type**
Caused by a combination of both primary injury or secondary effects

- Arthritis
- Postherpetic neuralgia
- Neuropathic low back pain

**Neuropathic Pain**
Initiated or caused by primary lesion or dysfunction in the nervous system

- CRPS*
- Trigeminal neuralgia
- Central post-stroke pain
- Distal polyneuropathy (eg, diabetic, HIV)

*Complex regional pain syndrome*
Importance of Pain Assessment

Pain is a significant predictor of morbidity and mortality.

- Screen for red flags requiring immediate investigation and/or referral
- Identify underlying cause
  - Pain is better managed if the underlying causes are determined and addressed
- Recognize type of pain to help guide selection of appropriate therapies for treatment of pain
- Determine baseline pain intensity to future enable assessment of efficacy of treatment

Locate the Pain

Body maps are useful for the precise location of pain symptoms and sensory signs.*

*In cases of referred pain, the location of the pain and of the injury or nerve lesion/dysfunction may not be correlated.

Determine Pain Intensity

Simple Descriptive Pain Intensity Scale

No pain | Mild pain | Moderate pain | Severe pain | Very severe pain | Worst pain

0–10 Numeric Pain Intensity Scale

0 No pain | 1 | 2 | 3 | 4 | 5 Moderate pain | 6 | 7 | 8 | 9 | 10 Worst possible pain

Faces Pain Scale – Revised


Evaluate Impact of Pain on Functioning

Pain

- Central sensitization/dysfunctional pain
- Nociceptive pain
- Neuropathic pain

Anxiety and depression

Sleep disturbances

Be Alert for Red Flags

Evaluate for patients presenting with pain the presence of **red flags**!

Initiate appropriate investigations/management or refer to specialist

Deciding on the Best Course of Treatment for the Patient

Collaborative Care

Patient as the ultimate manager of his/her illness

Family

Patient

General practitioner ± other health care professional(s)

Goals in Pain Management

• Involve the patient in the decision-making process
• Agree on realistic treatment goals **before** starting a treatment plan

*Optimized pain relief  Improved function*

*Minimized adverse effects*

Multimodal Treatment of Pain Based on Biopsychosocial Approach

- Pharmacotherapy
- Stress management
- Interventional pain management
- Biofeedback
- Education
- Complementary therapies
- Sleep hygiene
- Physical therapy
- Occupational therapy
- Lifestyle management

Non-pharmacological Interventions

- Non-pharmacological interventions are commonly used in clinical practice
- Establishing reliable evidence of efficacy and effectiveness can be challenging in terms of design and interpretation of studies

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>• Hypnosis</td>
</tr>
<tr>
<td></td>
<td>• Relaxation</td>
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<tr>
<td></td>
<td>• Cognitive behavioral therapy</td>
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<tr>
<td>Physical</td>
<td>• Acupuncture</td>
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<tr>
<td></td>
<td>• Transcutaneous electrical nerve stimulation</td>
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<tr>
<td></td>
<td>• Healing touch and massage</td>
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<tr>
<td></td>
<td>• Occupational therapy</td>
</tr>
<tr>
<td>Clinical process</td>
<td>• Pain assessment</td>
</tr>
<tr>
<td></td>
<td>• Physician advice and communication</td>
</tr>
<tr>
<td></td>
<td>• Education</td>
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</tbody>
</table>

WORLD HEALTH ORGANISATION
ANALGESIC LADDER

Pain threshold

Pain tolerance

0 1 2 3 4 5 6 7 8 9 10

mild moderate severe

Paracetamol or NSAID ± adjuvant analgesic

NSAID ± adjuvant analgesic ± weak opioid (codeine)

Strong opioid ± NSAID ± adjuvant analgesic

chronic pain

pain persists or increases
What are NSAIDs (nsNSAIDs/coxibs)?

**NSAID = Non-Steroidal Anti-Inflammatory Drug**

- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications:

<table>
<thead>
<tr>
<th>Examples of nsNSAIDs:</th>
<th>Examples of Coxibs:</th>
</tr>
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<tbody>
<tr>
<td>– Diclofenac</td>
<td>– Celecoxib</td>
</tr>
<tr>
<td>– Ibuprofen</td>
<td>– Etoricoxib</td>
</tr>
<tr>
<td>– Naproxen</td>
<td>– Parecoxib</td>
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</table>

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug
How do nsNSAIDs/coxibs work?

**COX-1 (constitutive)**

- **BLOCK**
- **Prostaglandins**
- **Gastrointestinal cytoprotection, platelet activity**

**COX-2 (induced by inflammatory stimuli)**

- **BLOCK**
- **Prostaglandins**
- **Inflammation, pain, fever**
- **Pain relief**

**Arachidonic acid**

**Coxibs**

**nsNSAIDs**

- **BLOCK**

*Coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug
nsNSAID = non-specific non-steroidal anti-inflammatory drug

How Opioids Affect Pain

Modify perception, modulate transmission and affect transduction by:

- Altering limbic system activity; modify sensory and affective pain aspects
- Activating descending pathways that modulate transmission in spinal cord
- Affecting transduction of pain stimuli to nerve impulses

Mechanism-Based Pharmacological Treatment of Neuropathic Pain

Medications affecting peripheral sensitization:
- Capsaicin
- Local anesthetics
- TCAs

Medications affecting descending modulation:
- SNRIs
- TCAs
- Tramadol, opioids

Medications affecting central sensitization:
- $\alpha_2\delta$ ligands
- TCAs
- Tramadol, opioids

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation.

Assessment of Pain Pathophysiology Can Help Guide Appropriate Medication Therapy

**Opioids**
For management of **moderate** to **severe** pain in appropriate patients

Most opioid treatment guidelines for chronic pain recommend use for patients after inadequate response to non-opioid therapy*

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**Acetaminophen**
**nsNSAIDs/coxibs**

**Neuropathic and central sensitization/ dysfunctional pain**

---

*Lack of response to non-opioid Tx*

---

**α₂δ ligands**
**Antidepressants**

---

*Mild       Moderate    Severe

*Selected on the basis of the pathophysiology of patient’s pain, provided there are no contraindications for its use
Coxib = COX-2-specific inhibitor;
nsNSAID = non-specific non-steroidal anti-inflammatory drug
Analgesics Affect Different Parts of the Pain Pathway

Coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug
Key Messages

- Pain is a common yet complex biopsychosocial phenomenon that affects every aspect of a patient’s life
- Pain can be classified into 3 main types according to pathophysiology (found separately or together/mixed type):
  - Pain due to inflammation or tissue damage (nociceptive pain)
  - Pain due to lesion or disease of somatosensory system (neuropathic pain)
  - Pain due to “central sensitization/dysfunctional pain” (terminology in flux)
- The type of pain pathophysiology can guide us to select rational, mechanism-based treatment options
- Optimal management often requires: identifying the red flags, treating the cause and combining pharmacological, biological, psychological/social and interventional techniques