



## **Pain Pathophysiology Unraveled**

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### **Disclosures**

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- Nothing to disclose



## Learning Objectives

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- Differentiate between nociceptive and neuropathic pain
- Describe the process of pain transmission
- Identify the specific pain pathways that can be acted upon by common pharmacotherapy classes

**Pain**week.

## Classification of Pain

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- Good pain vs bad pain



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## Good Pain

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- **Nociceptive pain:** purposeful pain
  - **Eudynia:** being in pain linked to normal tissue function or damage
  - Non-maldynic pain
  - Adaptive

**Pain**week.

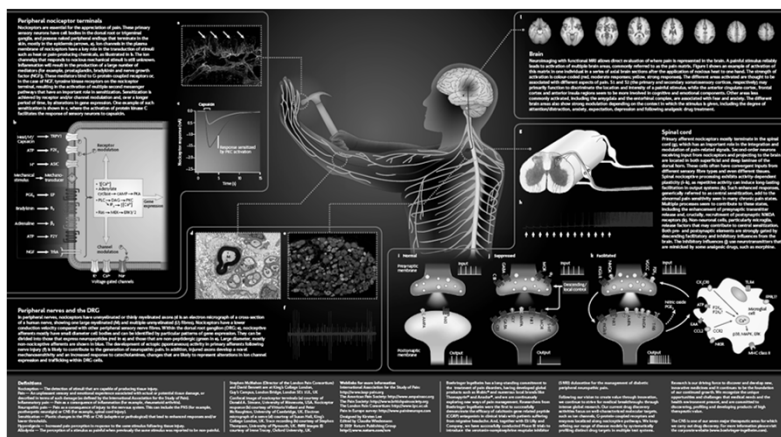
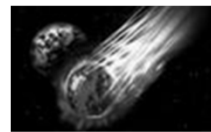
## Bad Pain

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- **Neuropathic pain:** non-purposeful pain
  - **Maldynia:** pain linked to disorder, illness, or damage
  - i.e may be abnormal, unfamiliar pain, assumed to be caused by dysfunction in PNS or CNS

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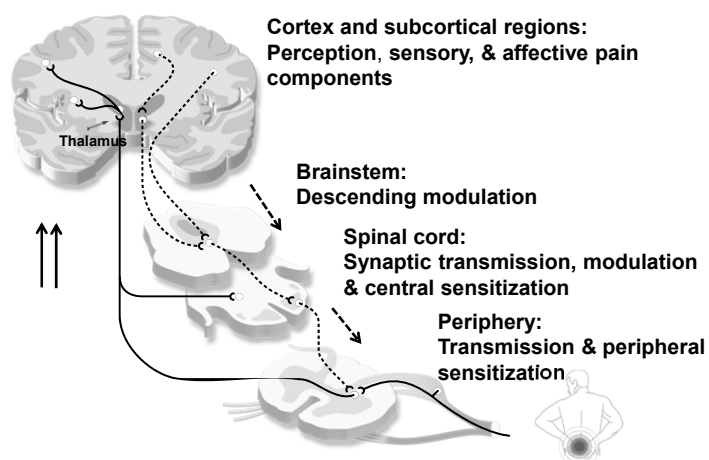
# Pain Mechanisms



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Adapted from Nature Reviews – Neuroscience, Stephen McMahon & David Bennett, 2007.

## General Anatomy of Pain

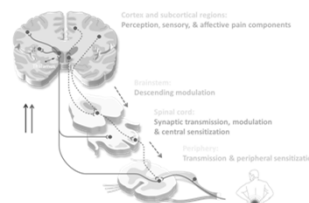


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Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 73(4):638-652.

## Pain Roadmap: Peripheral and Central Nervous System Landmarks

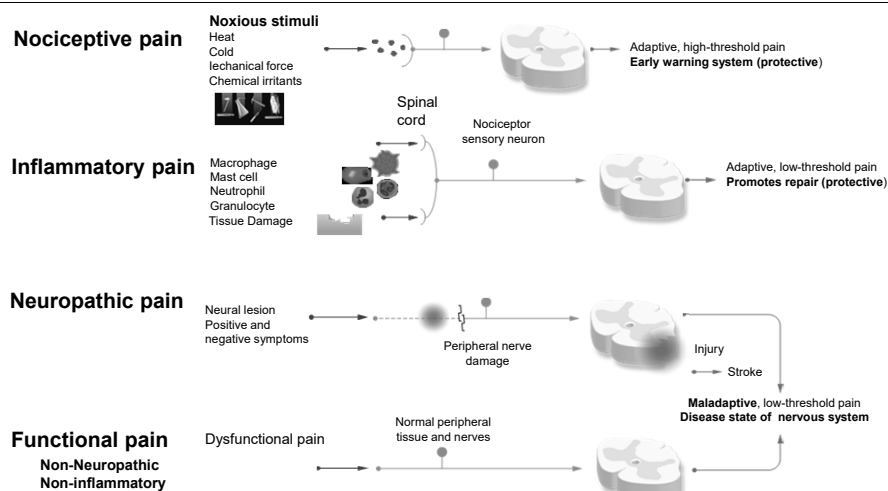
- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (i.e. occurring in real time)
- Adapts or changes in response to function—“neuroplasticity”



1. Gardner EP, et al. In: Kandel E, et al, eds. *Principles of Neural Science*. 4th ed. McGraw-Hill Medical; 2000; chapters 21-23.

**PainWeek**

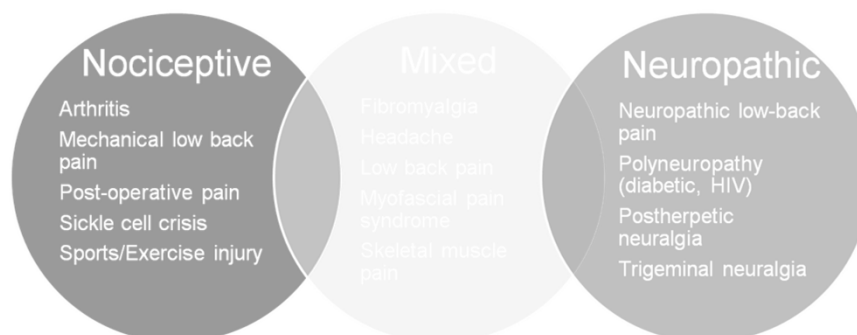
## Common Types of Pain



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Adapted from: Woolf CJ. *Ann Intern Med*. 2004;140:441-451.

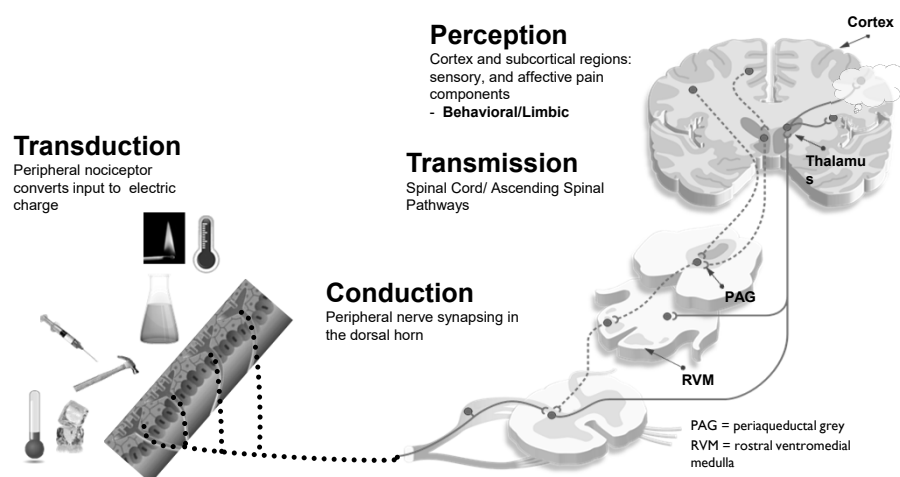
## Nociceptive vs Neuropathic Pain



1. Portenoy RK, Kanner RM. In: Portenoy RK, et al, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Company;1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: McGraw-Hill Companies Inc; 2000:8-9.

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## Pain Pathway Steps



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Adapted from Scholtz J, Woolf CJ, Nat Neuroscience, 2002;5:1062-1067

## Molecular Elements: Peripheral—Central

### Transduction

TRPV1, TRPV2, TRPV3,  
TRPM8  
ASIC, DRASIC  
MDEG, TREK-1  
BK<sub>1</sub>, BK<sub>2</sub>  
P2X<sub>3</sub>

### Membrane excitability of peripheral afferents

Na<sub>v</sub> 1.8, Na<sub>v</sub> 1.9  
K<sup>+</sup> channel

### Peripheral sensitization

NGF, TrkA  
TRPV1  
Na<sub>v</sub> 1.8  
PKA, PKC isoforms, CaMK IV  
Erk 1/2, p38, JNK  
IL-1B, cPLA<sub>2</sub>, COX2, EP1, EP3,  
EP4  
NF- $\kappa$ B

### Synaptic Transmission

#### Presynaptic

VGCC  
Adenosine-R  
(mGlu-R)

#### Postsynaptic

AMPA/kainite-R, NMDA-R, mGlu-R  
NK1  
Na<sub>v</sub> 1.3  
K<sup>+</sup> channel

### Central Inhibition

GABA, GABA<sub>A</sub>-R, GABA<sub>B</sub>-  
R  
Glycine-R  
NE, 5-HT  
Opioid receptors  
CB1

### Signal transduction

PKA, PKC isoforms  
ERK, p38, JNK

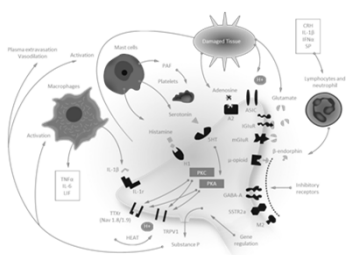
### Gene expression

c-fos, c-jun, CREB,  
DREAM

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Adapted from Scholz J, Woolf CJ, Nature Neuroscience supplement Vol 5, 2002

## Transduction: Processing at Peripheral Nerve Endings

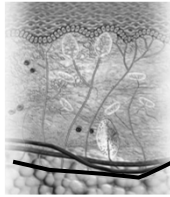


- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
  - Receptors activated directly by stimuli
  - Injury/inflammatory response

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Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA: Saunders; 2011: chapter 2.

## How is Pain Transduced?



- Nociception

- Mechanical
- Thermal
- Chemical

- Mediators

- Prostaglandins
- Leukotrienes
- Substance P
- Histamine
- Bradykinin
- Serotonin
- Hydroxyacids
- Reactive oxygen species
- Inflammatory cytokines and chemokines

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## Conduction

- Conduction impulses from primary nociceptors to the spinal cord (dorsal horn) along the peripheral nerve



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## Primary Nociception

### ▪ A-delta fibers

- Small receptive fields
- Thermal & mechanical
- Myelinated
- Rapidly conducting
  - 10-30 m/sec
- Large diameter



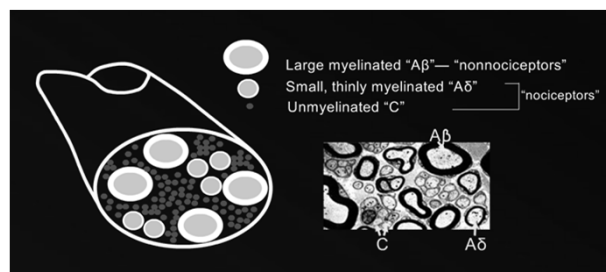
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### ▪ C-fibers

- Broad receptive fields
- Polymodal
- Unmyelinated
- Slower conducting
  - .5-2.0 m/sec
- Cross sensitized
- Small diameter



## Peripheral Pain Nociceptors

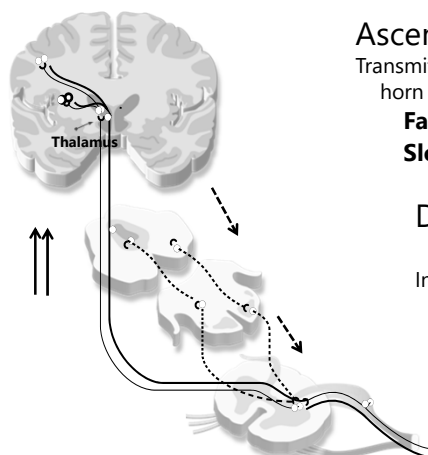


**Aβ** - muscle spindle secondary endings, touch, and kinesthesia.  
**Aδ** - pain, temperature, crude touch, and pressure.

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Bashbaum A, Jessell T, The perception of Pain, In Kendal E, Schwartz J, Principles of Neural Science 4<sup>th</sup> ed, New York, McGraw Hill, 2000, 482-483.

## Transmission & Modulation



**Ascending nociceptive pathways**  
Transmitting nociceptive impulses from the dorsal horn to supraspinal targets

**Fast (green)** Neospinothalamic

**Slow (yellow)** Paleospinothalamic

**Descending inhibitory tracts (blue)**

Increase or decrease volume control of incoming nociceptive signals reaching the brain

5-HT - Serotonin

NE - Norepinephrine

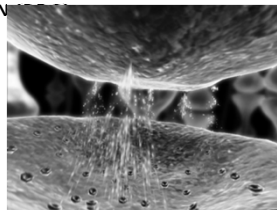
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Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23,73(4):638-652.

## How is Pain Conducted and Transmitted?



**DORSAL ROOT GANGLION**



### Excitatory Transmitters

- Substance P
- Calcitonin gene related peptide
- Aspartate, Glutamate

### Inhibitory Transmitters (descending inhibitory pathways)

- GABA
- Glycine
- Somatostatin
- $\alpha 2$  agonists

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## Role of Neuronal Plasticity in Pain

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- Nervous system changes in
  - Neuronal structure
  - Connections between neurons
  - Quantity/properties of neurotransmitters, receptors, ion channels
- Decreases body's pain inhibitory systems (increased pain)
- Injury, inflammation, and disease are culprits
- Produces short-term and permanent changes
- Pivotal to the development of hypersensitivity of inflammatory pain
  
- Enables NS to modify its function according to different conditions or demands placed upon it



## How Acute Pain Becomes Chronic

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- Peripheral sensitization
  - Tissue damage releases sensitizing “soup” of cytokines and neurotransmitters
  - COX-mediated PGE2 release
  - Sensitized nociceptors exhibiting a decreased threshold for activation and increased rate of firing
- Central sensitization—Resulting from noxious input to the spinal cord
  - Resulting in hyperalgesia and allodynia



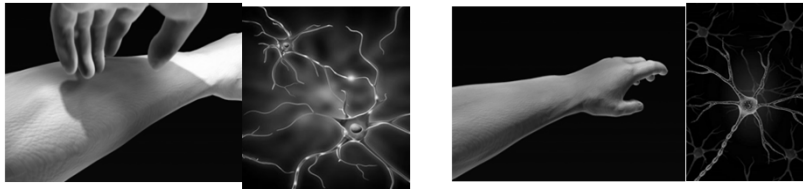
## Definitions

### ▪ Hyperalgesia

- Lowered threshold to different types of noxious stimuli

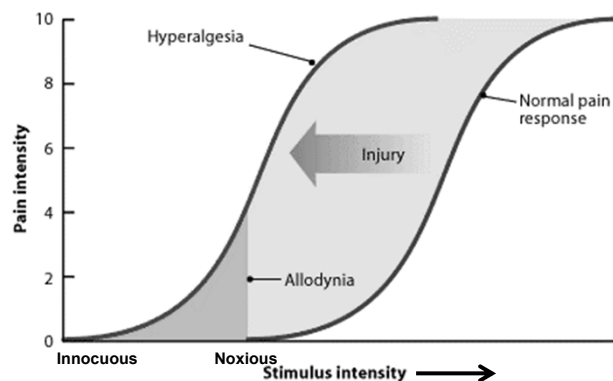
### ▪ Allodynia

- Painful response to what should normally be non-painful stimuli



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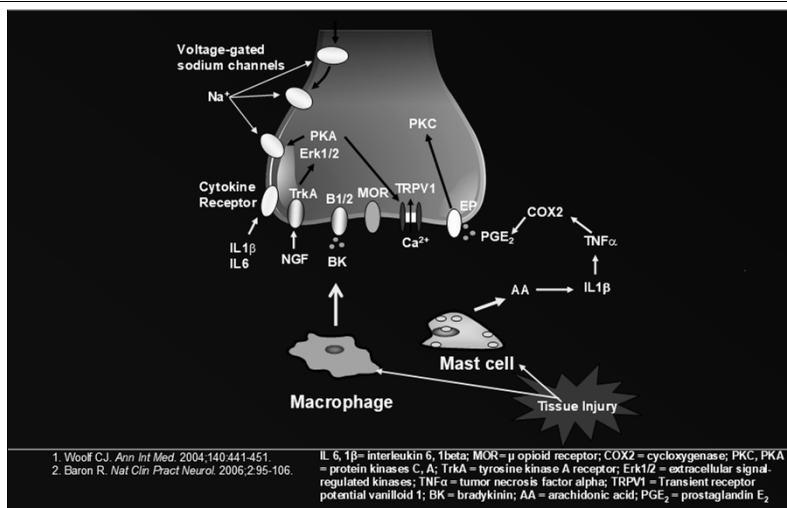
## Neuroplasticity in Pain Processing



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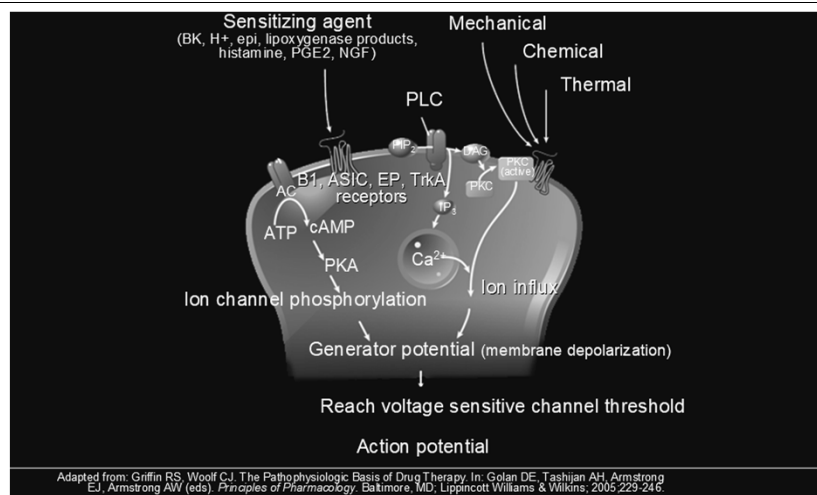
1. Woolf CJ, Salter MW. *Science*. 2000;288:1765-1768.
2. Basbaum AI, Jessell TM. The perception of pain. In: Kandel ER, Schwartz JH, et al. eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill; 2000:479.
3. Cervero F, Laird JMA. *Pain*. 1996;68:13-23.

## Neuroplasticity in Peripheral Pain Transmission



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## Peripheral Sensitization



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## How Acute Pain Becomes Chronic

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- Central sensitization
  - Activation
    - “Wind up” of dorsal horn nociceptors
  - Modulation
    - Excitatory/Inhibitory neurotransmitters
  - Decreased central inhibition of pain transmission
  - Prime role in chronic pain, particularly neuropathic pain



## Definitions

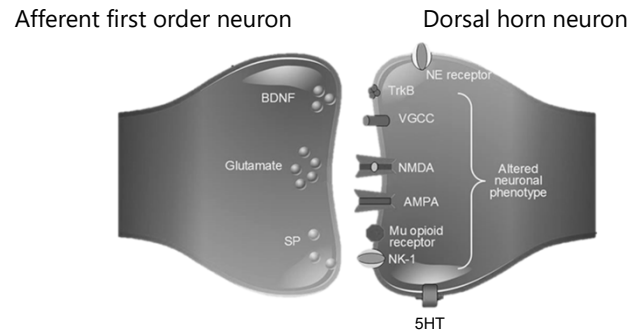
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- Wind Up
  - Causes long-term changes in nociceptive neurons, which become hyperexcitable such that they respond to lower stimuli
    - NMDA-type glutamate receptors play an important role in this process<sup>1,2,3,4</sup>
  - Prolonged opening of the ion channels enables greater influx of calcium and sodium across the post-synaptic membrane and greater excitation of nociceptive neurons<sup>2,3</sup>



1. Kandel ER, Schwartz JH, Jessell TM, editors. Principles of Neural Science (Fourth Edition). New York: McGraw Hill (Health Professions Division). 2000;472-491.  
 2. Millan MJ. Progress in Neurobiology 1999;57:1-164.  
 3. Dickenson AH. Brit J Anaesthesia 1995;75:193-200.  
 4. Suzuki R and Dickenson AH. Neuroreport 2000;11:R17-21.

## Central Sensitization



NK-1 = Neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartic acid; VGCC = voltage gated sodium channel; TrkB = tropomyosin receptor kinase B; BDNF = Brain derived neurotrophic factor; SP = substance P

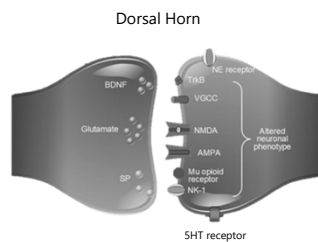
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Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

## Central Sensitization (cont'd)

### Key Influences upon signal propagation

- Excitatory neurotransmitters
  - Substance P, CGRP, glutamate
- NMDA channel activity
  - Glutamate binding
  - Altering channel activity
- Descending inhibitory tracts
  - NE/serotonin (5HT)
- Mu opioid receptor

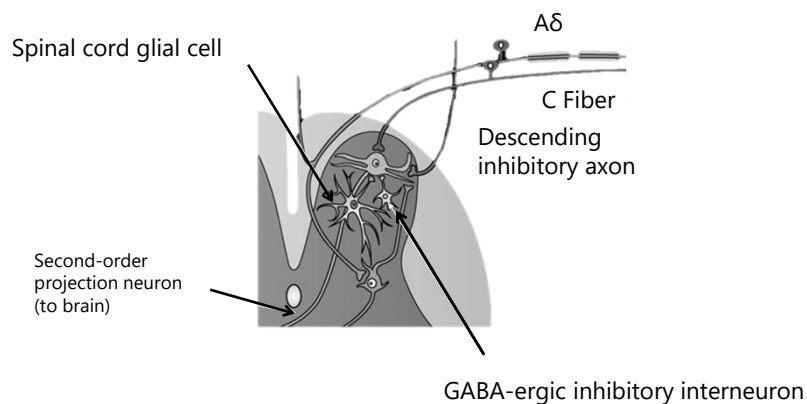


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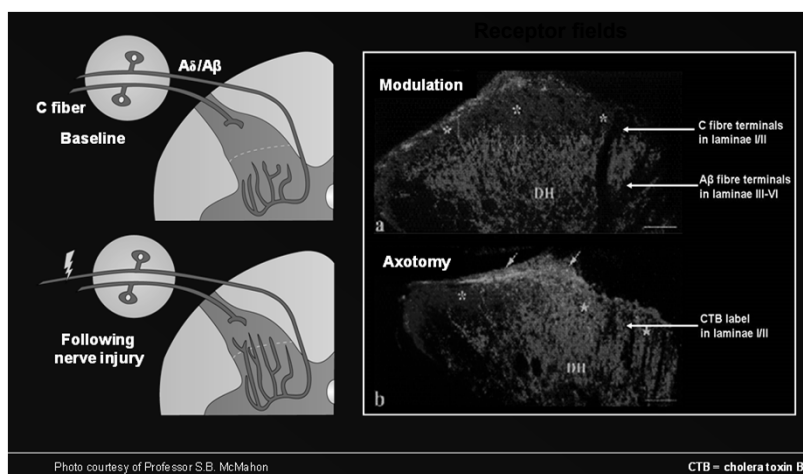
## Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing<sup>1,2</sup>



**PainWeek**

Adapted from 1. Baron R. Mechanisms of disease: neuropathic pain-a clinical perspective. *Nat Clin Pract Neurology*. 2006;2:95-106.  
2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Int Med*. 2004;140:441-451.

## Neuroplasticity: Neural Reorganization

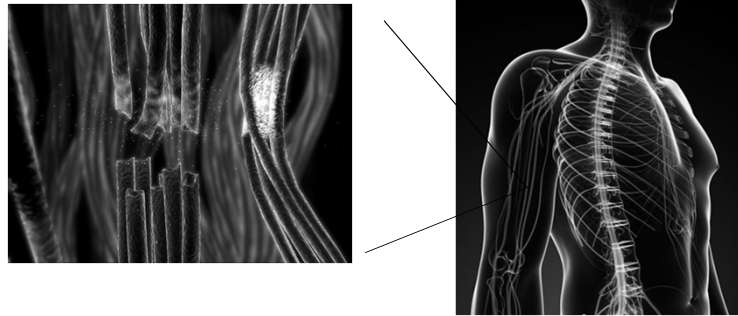


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CTB = cholera toxin B



## Neuroplasticity: Cross Talk



CTB = cholera toxin B

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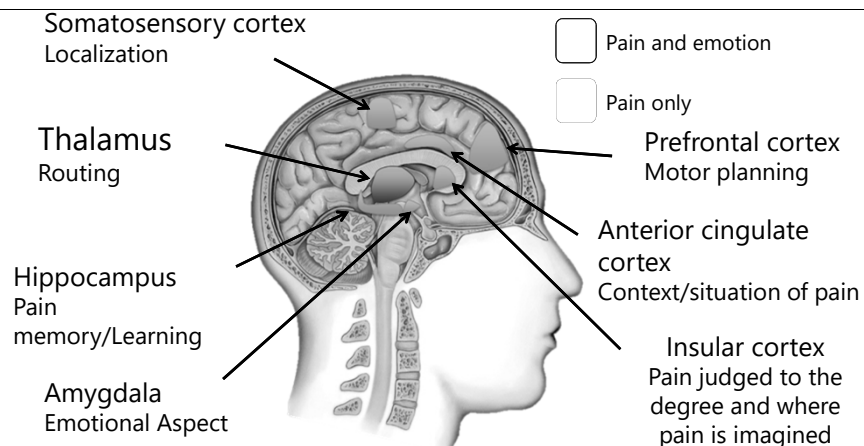
## Central Sensitization: Neuroplasticity in Spinal Cord Processing

- Definition: Altered function of neurons or synaptic activity
- Mechanisms of central sensitization may include:
  - Changes effecting glutamate/NMDA receptors activity
    - Reduced threshold for activation
    - Increased availability of glutamate
    - Increased influx of  $\text{Na}^+/\text{Ca}^+$  (receptor open longer)
  - Modulation—excitatory/Inhibitory neurotransmitters
  - Decreased tone—descending inhibitory pathways<sup>2</sup>
  - Activation/migration of glial cells into the spinal cord<sup>3</sup>
  - Changes in the thalamus and primary somatosensory cortex<sup>4</sup>

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1. Mannion RJ, Woolf CJ: *Clin J Pain*. 2000;16(3):S151-S153. 2. Ossipov MH, et al. *Ann NY Acad Sci*. 2000;909:12-24.  
3. Wieseler-Frank J, et al. *Neurosignals*. 2005;14:166-174. 4. Guilbaud G, et al. *Exp Brain Res*. 1992;92:227-245.

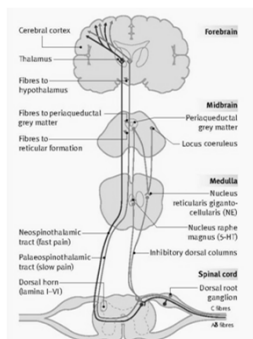
## Brain Regions Involved in Pain Processing



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Apkarian AV et al, Eur J Pain 2005;9:463-484

## Analgesics That Modify Pain Processes



### Transduction

- NSAIDs
- Antihistamines
- Membrane stabilizing agents
- Local anesthetic cream
- Opioids
- Bradykinin & Serotonin antagonists

### Transmission/Modulation

- Spinal opioids
- $\alpha_2$  agonists
- NMDA receptor antagonists
- NSAIDs
- NO inhibitors
- $K^+$  channel openers

### Perception

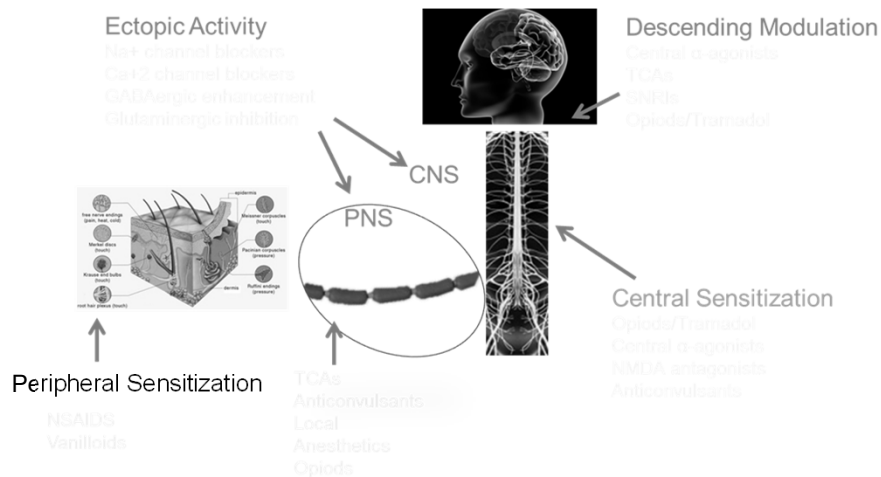
- Parenteral opioids
- $\alpha_2$  agonists
- General anesthetics

### Conduction

- Local anesthetics
  - Peripheral nerve, plexus, epidural block

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## Pharmacological Targets in Pain



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Woolf C, Max M Anesthesiology 2001

## The Chronic Pain Armamentarium

### Nonopioids

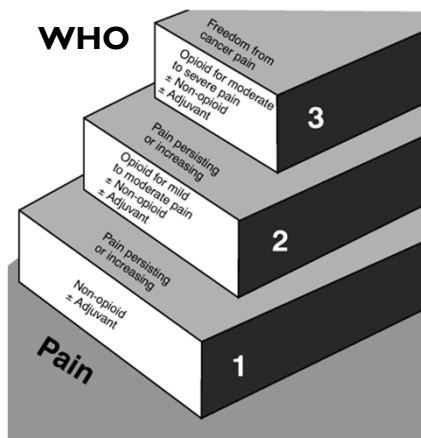
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

### Opioids

- Mu-opioid agonists
- Mixed agonist-antagonists

### Adjuvant analgesics

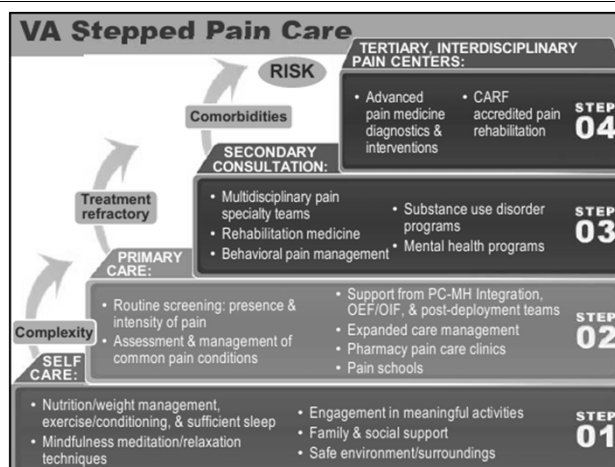
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics



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JC Ballantyne Oncologist 2003;8(6):567-75. © AlphaMed Press; WHO. 2005.

## VA DoD Stepped Pain Care Model

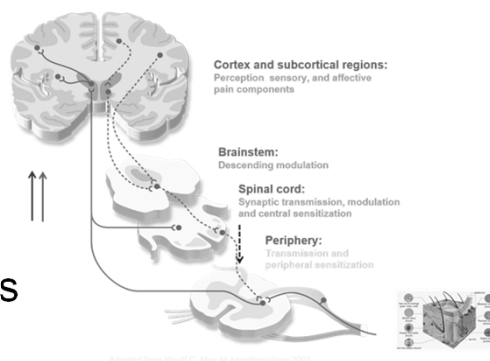


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PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing:  
A Military Perspective, Buckenmaier C (COL) ret, Aug 24, 2016  
*JAMA Intern Med.* 2015;175(5):682-689. doi:10.1001/jamainternmed.2015.97

## Common Pharmacologic Therapies

- Acetaminophen
- NSAIDS
- Antiepileptics
- TCAs
- SNRIs
- Topicals
- Muscle relaxants
- Opioids



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## Nonopioids: Acetaminophen

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### Example

- Acetaminophen

### Mechanism of action

- Inhibits prostaglandin production in CNS; antipyretic activity
- No effect on blocking peripheral prostaglandin production; no anti-inflammatory or antirheumatic activity

### FDA Warning

- Potential severe liver damage if over-used
- Stevens-Johnson Syndrome and toxic epidermal necrolysis



## Nonopioids: NSAIDs

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### Examples

- Acetylated (aspirin); nonacetylated (diflunisal); acetic acid (diclofenac); propionic acid (naproxen); fenamic acid (mefenamic acid); enolic acids (piroxicam); nonacidic (nabumetone); ibuprofen, selective COX-2s (celecoxib)

### Mechanism of action

- Exhibit both peripheral and central effects; antiinflammatory and analgesic effects
- Inhibition of cyclooxygenase and prostaglandin production
- Inhibition of leukotriene B4 production
- Lipoxins (signaling resolution of inflammation)



## Opioids

### Examples

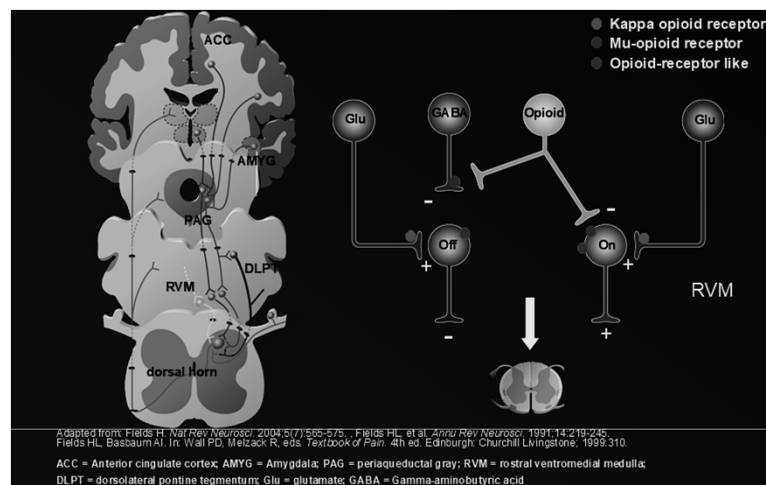
- Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone, meperidine, codeine, methadone, tramadol

### Mechanism of action

- Bind to opioid receptors in the central nervous system (CNS) to inhibit transmission of nociceptive input from periphery to spinal cord
- Activate descending pathways that modulate transmission in spinal cord
- Alter limbic system activity; modify sensory and affective pain aspects

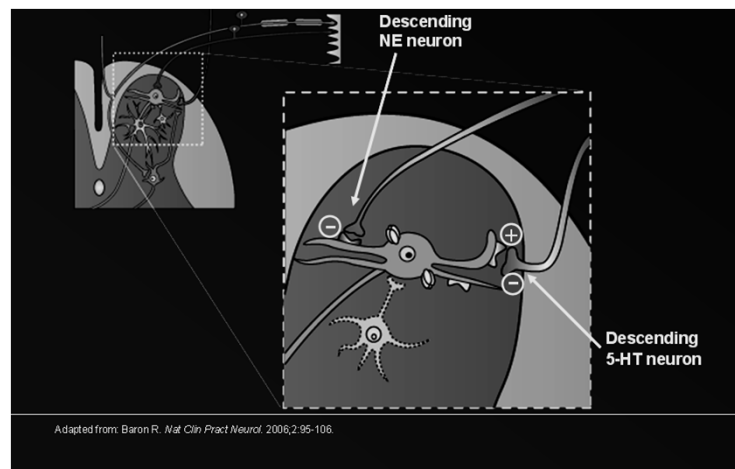
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## Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



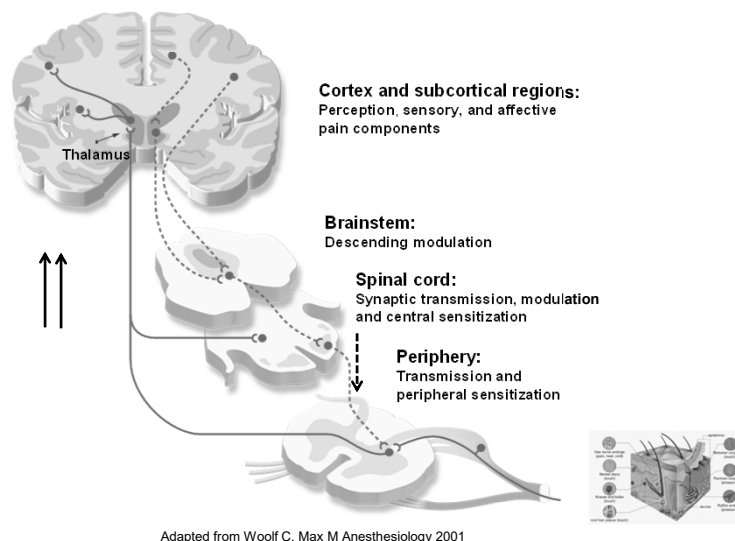
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## Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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## Mechanism of Action: Opioids



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## Adjuvant Analgesics: Tricyclic Antidepressants

### Examples

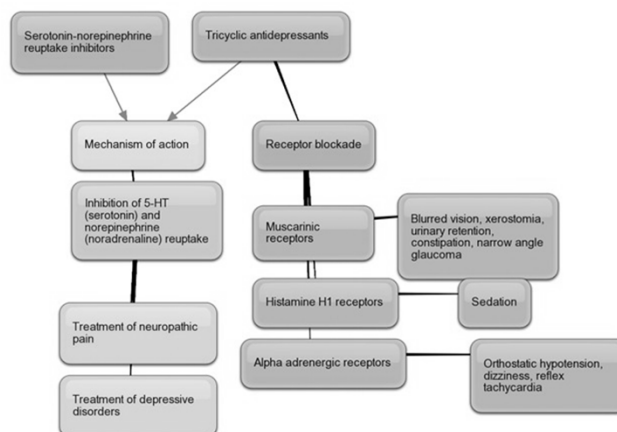
– Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

### Mechanism of action

- Reduction in action potential firing of sodium channel activity
- Inhibition of reuptake of NE and 5-HT
- Analgesia is independent of antidepressant function
- High side effect profile (tolerability)
  - cardiotoxic (overdose)

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## TCAs and SNRIs Pharmacological Properties



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<http://pharmacologycorner.com>



## SSRIs (Selective Serotonin Reuptake Inhibitors)

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### Examples

– Citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline

### Mechanism of action

– Selectively inhibit 5-HT reuptake without affecting NE

*Therefore, no pain relief expected!*

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## Serotonin

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### ▪ International Union of Pure and Applied Chemistry nomenclature

– **5-Hydroxytryptamine (5-HT)**

– Monoamine neurotransmitter, biochemically derived from tryptophan

– **Receptors** are a group of G protein-coupled receptors (GPCRs) and ligand-gated ion channels (LGICs) found in the central and peripheral nervous systems

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## Serotonin/5-HT Receptors

Family	Type	Mechanism	Potential
5-HT <sub>1</sub>	G <sub>i</sub> /G <sub>o</sub> -protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT <sub>2</sub>	G <sub>q</sub> /G <sub>11</sub> -protein coupled.	Increasing cellular levels of IP <sub>3</sub> and DAG.	Excitatory
5-HT <sub>3</sub>	Ligand-gated Na <sup>+</sup> and K <sup>+</sup> cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT <sub>4</sub>	G <sub>s</sub> -protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT <sub>5</sub>	G <sub>i</sub> /G <sub>o</sub> -protein coupled. <sup>[4]</sup>	Decreasing cellular levels of cAMP.	Inhibitory
5-HT <sub>6</sub>	G <sub>s</sub> -protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT <sub>7</sub>	G <sub>s</sub> -protein coupled.	Increasing cellular levels of cAMP.	Excitatory

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[http://en.wikipedia.org/wiki/5-HT\\_receptor](http://en.wikipedia.org/wiki/5-HT_receptor)

## Serotonin/5-HT Receptors (cont'd)

- 5-HT<sub>1a</sub> (Blood Vess/CNS)
  - Addiction
  - Aggression
  - Anxiety
  - Appetite
  - BP
  - Cardiovascular function
  - Emesis
  - Heart rate
  - Impulsivity
  - Memory
  - Mood
  - Nausea
  - Nociception
  - Penile erection
  - Pupil dilatation
- 5-HT<sub>1a</sub> (*cont*)
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation
- 5-HT<sub>5a</sub> & 5-HT<sub>6</sub> (CNS)
  - Locomotion
  - Sleep
  - Anxiety
  - Cognition
  - Learning
  - Memory
  - Mood

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[http://en.wikipedia.org/wiki/5-HT\\_receptor](http://en.wikipedia.org/wiki/5-HT_receptor)

## SNRIs (Serotonin/Noradrenaline Reuptake Inhibitors)

### Examples

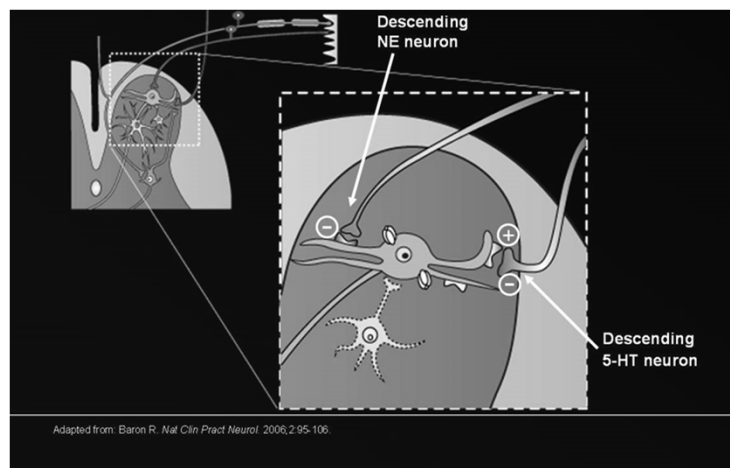
– Duloxetine, milnacipran, and venlafaxine

### Mechanism of action

- Block reuptake of 5-HT and NA
  - Better tolerated, lower tendency for drug-drug interactions, better overdose safety

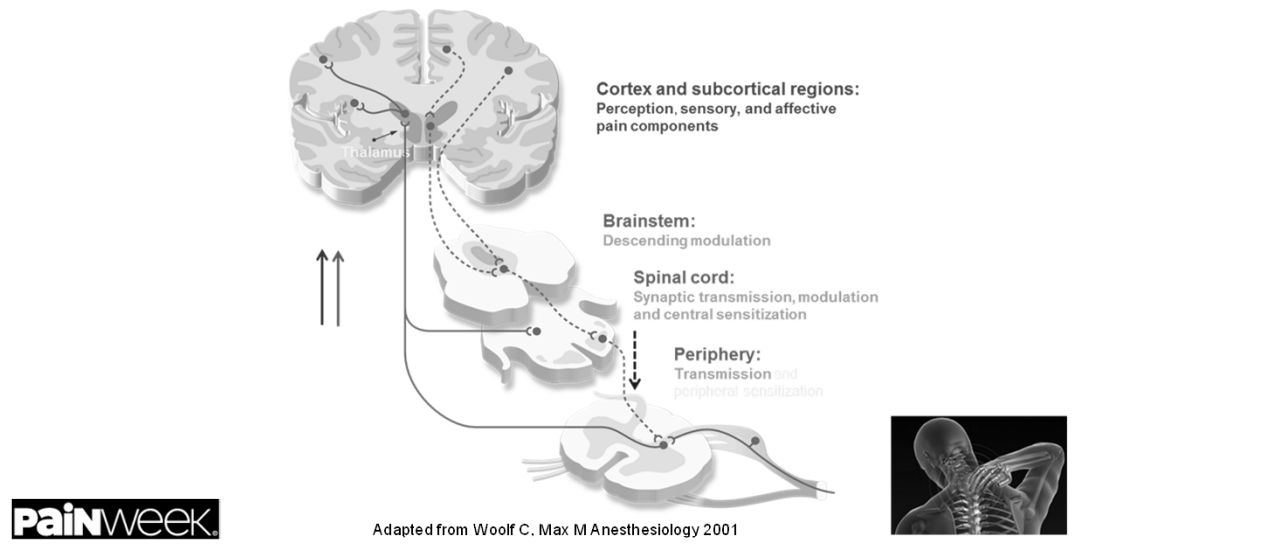
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## Modulation of Central Sensitization by 5-HT & NE Descending Pathways



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## Site of Action: SNRIs



## Adjuvant Analgesics: Antiepileptics

### Examples

- Gabapentin, pregabalin\*, carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine

### Mechanism of action

- Suppress neuronal hyperexcitability via
  - Reducing neuronal influx of sodium ( $\text{Na}^+$ ) and calcium ( $\text{Ca}^{++}$ )
  - Direct/indirect enhancement of GABA inhibitory effects
  - Reduce activity of glutamate and/or blocking NMDA receptors
  - Binds the  $\alpha 2\delta$  subunit of voltage gated  $\text{Ca}^{++}$  channels, inhibit NT release

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## Muscle Relaxants

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- Decrease tone of skeletal muscles
- Subclasses
  - Neuromuscular blockers
    - Act at the neuromuscular junction
    - Often used in surgery to cause temporary paralysis
  - Spasmolytics
    - Centrally acting



## Muscle Relaxants: Spasmolytics

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- Enhancing the level of inhibition
  - Mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA
- Reducing the level of excitation
- Common examples
  - Cyclobenzaprine (TCA) methocarbamol, carisoprodol, tizanadine ( $\alpha$ -2 agonist), baclofen (GABA agonist), orphenadrine (benzodiazepine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisoprodol)



## Case Study

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- 54-year-old with 3 year history of neck, shoulder, and upper extremity pain following a lifting injury
  - Current medications
    - Fluoxetine
    - Milnacipran
    - Gabapentin
    - Clonazepam
    - Alprazolam
    - Robaxin
    - Tapentadol
    - Acetaminophen and propoxyphene
    - Zolpidem
    - Diclofenac topical
    - Acetaminophen



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## Importance for Understanding Pain Mechanisms

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- Allow for rational rather than empirical approach to pain control
- Foster the development of diagnostic tools to identify specific pain mechanisms
- Facilitate pharmacotherapies that act on specific pain pathways and mechanisms
- Reduce the number of pharmacotherapies and incidence of drug-related adverse events (rationale polypharmacy)
- Enhances use of non-pharmacologic treatments
- Improve overall patient care and outcome
  - Tailoring treatment based on the individual patient and pain type
- Do not forget to look for the spear

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