PAINWEEK

## Pain Pathways Made Simple

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## Disclosures

- Nothing to Disclose

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## Learning Objectives

- 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

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## Classification of Pain

- Good pain vs bad pain

Clinical Pearl

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## Good Pain

- **Nociceptive pain**: purposeful pain
  - **Eudynia**—pain linked to normal tissue function or damage
  - Nonmaldynic pain
  - Adaptive

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## Bad Pain

- **Neuropathic pain**: nonpurposeful pain
  - **Maldynia**—pain linked to disorder, illness or damage
  - ie, may be abnormal, unfamiliar pain, assumed to be caused by dysfunction in PNS or CNS

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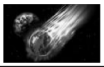
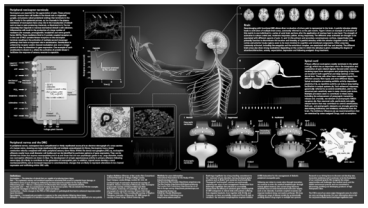
## Pain Mechanisms





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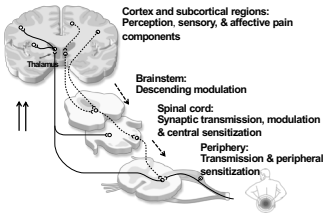
Adapted from Nature Reviews – Neuroscience, Stephen McMahon & David Bennett, 2007.

## General Anatomy of Pain




**Cortex and subcortical regions:**
**Perception, sensory, & affective pain components**

**Brainstem:**
**Descending modulation**

**Spinal cord:**
**Synaptic transmission, modulation & central sensitization**

**Periphery:**
**Transmission & peripheral sensitization**

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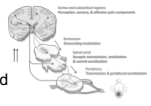
- Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012; 23;73(4):638-652

## 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 (ie, 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*. 4th ed. McGraw-Hill Medical; 2000; chapters 21-23.

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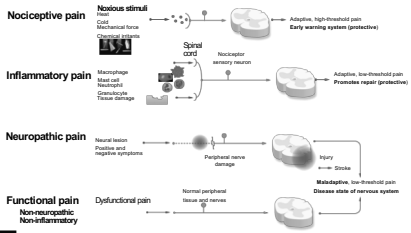
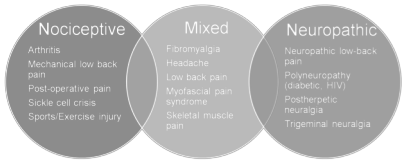
## Common Types of Pain



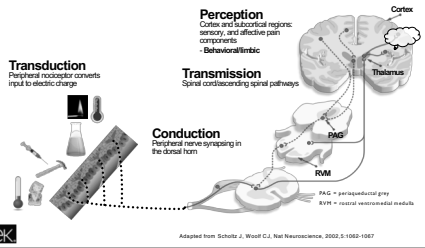

Adapted from: Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

## Nociceptive vs Neuropathic Pain



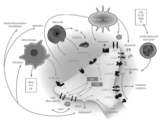

1. Portenoy RK, Kanner RM. In: Portenoy RK, et al, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Company;1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: McGraw-Hill Companies Inc; 2000:8-9.

## Pain Pathway Steps




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

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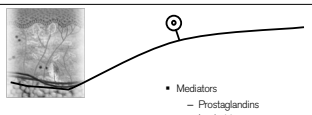
Adapted from Dougherty PM, et al. Neurochemistry of somatosensory and pain processing. In: Benzon H, et al, eds. *Essentials of Pain Medicine*. Philadelphia, PA: Saunders; 2011: chapter 2.

## 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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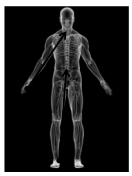
## Conduction

- 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

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

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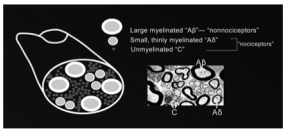
## Peripheral Pain Nociceptors




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

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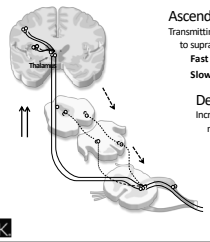
Bashbaum A, Jessell T, The perception of Pain, In Kendal E, Schwartz J, Principles of Neural Science 4th ed, New York, McGraw Hill, 2000, 482-483.

## Transmission & Modulation




Ascending nociceptive pathways
Transmitting nociceptive impulses from the dorsal horn to supraspinal targets
**Fast** *(green)* neospinalthalamic
**Slow** *(yellow)* paleospinalthalamic

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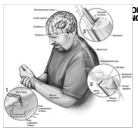
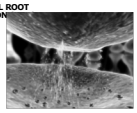
Adapted from Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012; 73(4):638-652.

## How is Pain Conducted and Transmitted?





- **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

- 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

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## How Acute Pain Becomes Chronic

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

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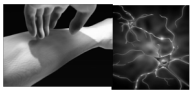
## Definitions

- **Hyperalgesia**
  - Lowered threshold to different types of noxious stimuli
- **Allodynia**
  - Painful response to what should normally be nonpainful stimuli



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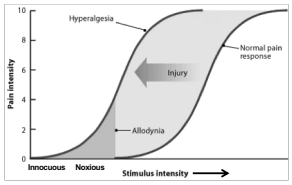
## Neuroplasticity in Pain Processing

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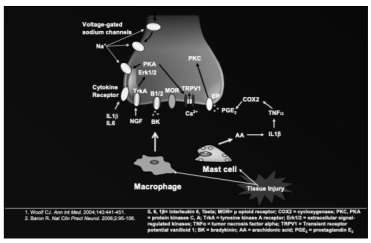
1. Woolf CJ, Salter MW. Science. 2000;288:1765-1769.
2. Ringkamp M, Meyer RA. The perception of pain. In: Kandel ER, Schwartz JH, et al, eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill; 2000:479.
3. Cervero F. *Lancet Neurol*. 2003;2:203-215.

## Neuroplasticity in Peripheral Pain Transmission




1. Woolf CJ. *Ann Int Med*. 2004;140:441-451.
2. Baron R. *Nat Clin Pract Neurol*. 2006;2:95-106.

IL, IL 1β= interleukin 6, 1beta; MOR= μ opioid receptor; COX2 = cyclooxygenase; PKC, PKA = protein kinases C, A; TRA = tyrosine kinase A receptor; ERK1/2 = extracellular signal-regulated kinase 1, 2; NGF = nerve growth factor; TRPV1 = transient receptor potential vanilloid 1; BK = bradykinin; AA = arachidonic acid; $PGE_2$ = prostaglandin $E_2$

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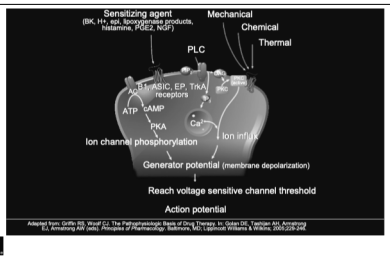
## Peripheral Sensitization




Adapted from: Griffin RS, Woolf CJ. The Pathophysiologic Basis of Drug Therapy. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW (eds). *Principles of Pharmacology*. Baltimore, MD: Lippincott Williams & Wilkins, 2005:228-242

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## Central Sensitization

- Activation
  - "Wind up" of dorsal horn nociceptors
- Modulation
  - Excitatory/Inhibitory neurotransmitters
- Decreased central inhibition of pain transmission
  - NE/5HT

Prime role in chronic pain, particularly neuropathic pain

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## Definitions

- 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[1,2,3,4]
  - Prolonged opening of the ion channels enables greater influx of calcium and sodium across the post-synaptic membrane and greater excitation of nociceptive neurons[2,3]

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.

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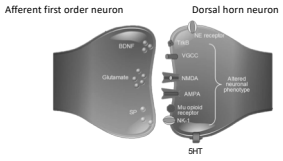
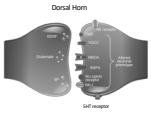
## Central Sensitization




NK-1 = neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyle 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

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

## Central Sensitization



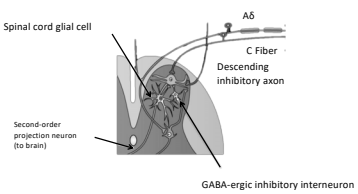

Key influences upon signal propagation

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

NK-1 = neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyle 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; CRGP = calcitonin gene related peptide

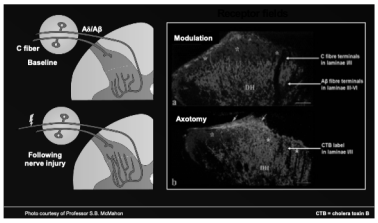
Adapted from Schlotz J, Woolf CJ. Nat Neuroscience. 2002;5:1062-1067

## Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing[1,2]




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




CTB = cholera toxin B

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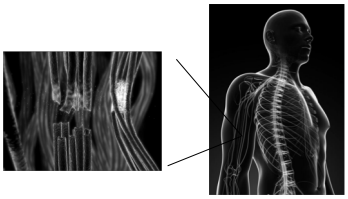
## Neuroplasticity: Cross Talk



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 affecting glutamate/NMDA receptors activity
    - Reduced threshold for activation
    - Increased availability of glutamate
    - Increased influx of $Na^+/Ca^+$ (receptor open longer)
  - Modulation—excitatory/Inhibitory neurotransmitters
  - Decreased tone—descending inhibitory pathways[2]
  - Activation/migration of glial cells into the spinal cord[3]
  - Changes in the thalamus and primary somatosensory cortex[4]

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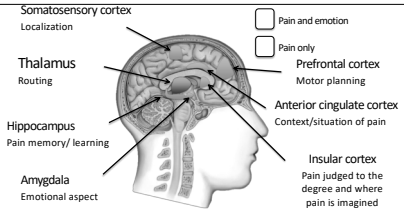
1. Mannion RJ, Woolf CJ. *Clin J Pain.* 2000;16(3):S151-S153. 2. Ossipov MH, et al. *Ann NY Acad Sci.* 2000;909:12-24.
3. Wieseler-Frank J, et al. *Neuroscignals.* 2005;14:166-174. 4. Guilbaud G, et al. *Exp Brain Res.* 1992;92:227-243.

## Brain Regions Involved in Pain Processing

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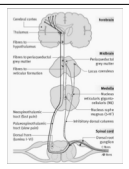
Apkarian AV et al, Eur J Pain 2005;9:463-484

## 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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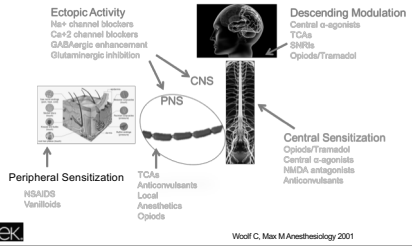
## Pharmacological Targets in Pain

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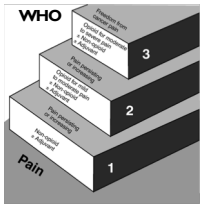
Woolf C, Max M Anesthesiology 2001

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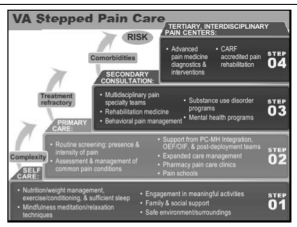
IC Ballantyne Oncologist 2003;8(6):567-75 © AlphaMed Press; WHO 2005

## VA DoD Stepped Pain Care Model

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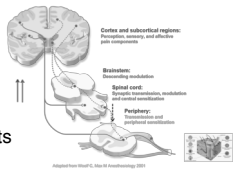
PCSS-O Webinar Implementation of the National Pain Strategy and Safer Opioid Prescribing: A Military Perspective, Buckenmaier C (COL) ret, Aug 24, 2016
*JAMA Intern Med.* 2015;175(5):682-689. doi:10.1001/jamainternmed.2015.87

## Common Pharmacologic Therapies

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

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## Nonopioids: Acetaminophen

*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 & toxic epidermal necrolysis

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## Nonopioids: NSAIDs

*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; anti-inflammatory and analgesic effects
- Inhibition of cyclooxygenase and prostaglandin production
- Inhibition of leukotriene B4 production
- Lipoxins (signaling resolution of inflammation)

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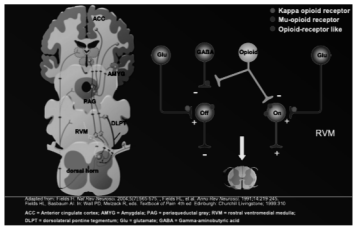
## Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response




ACC = Anterior cingulate cortex; AMYG = Amygdala; PAG = periaqueductal gray; RVM = rostral ventromedial medulla; DLPT = dorsolateral pontine tegmentum; Glu = glutamate; GABA = Gamma-aminobutyric acid

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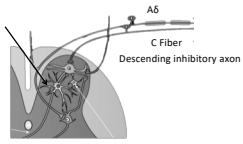
## Modulation of Central Sensitization by 5-HT & NE Descending Pathways

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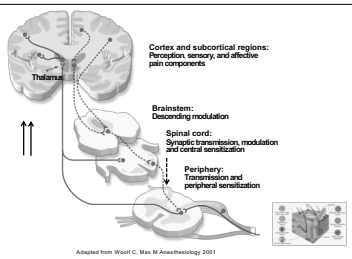
## Mechanism of Action—Opioids




Adapted from Woolf C, Max M Anesthesiology 2001

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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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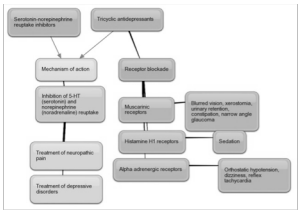
## TCAs and SNRIs Pharmacological Properties

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http://pharmacologycorner.com

## SSRIs (Selective Serotonin Reuptake Inhibitors)

*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

- 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-HT1 | $G_i/G_o$-protein coupled. | Decreasing cellular levels of cAMP. | Inhibitory |
| 5-HT2 | $G_q/G_{11}$-protein coupled. | Increasing cellular levels of IP3 and DAG. | Excitatory |
| 5-HT3 | Ligand-gated $Na^+$ and $K^+$ cation channel. | Depolarizing plasma membrane. | Excitatory |
| 5-HT4 | $G_s$-protein coupled. | Increasing cellular levels of cAMP. | Excitatory |
| 5-HT5 | $G_i/G_o$-protein coupled.[4] | Decreasing cellular levels of cAMP. | Inhibitory |
| 5-HT6 | $G_s$-protein coupled. | Increasing cellular levels of cAMP. | Excitatory |
| 5-HT7 | $G_s$-protein coupled. | Increasing cellular levels of cAMP. | Excitatory |

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http://en.wikipedia.org/wiki/5-HT_receptor

## Serotonin/5-HT Receptors

- 5-HT1a (blood ves/CNS)
  - Addiction
  - Aggression
  - Anxiety
  - Appetite
  - BP
  - Cardiovascular function
  - Emesis
  - Heart rate
  - Impulsivity
  - Memory
  - Mood
  - Nausea
  - Nociception
  - Penile erection
  - Pupil dilatation
- 5-HT1a *(cont'd)*
  - Respiration
  - Sexual behavior
  - Sleep
  - Sociability
  - Thermoregulation
- 5-HT5a & 5-HT6 (CNS)
  - Locomotion
  - Sleep
  - Anxiety
  - Cognition
  - Learning
  - Memory
  - Mood

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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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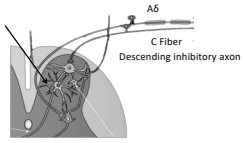


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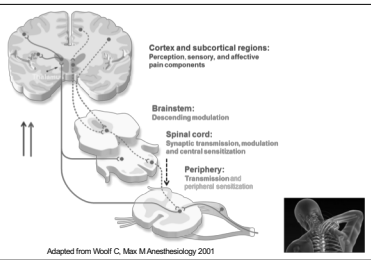
## Site of Action—SNRIs

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Adapted from Woolf C, Max M Anesthesiology 2001

## 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 (Na+) and calcium (Ca+ +)
  - Direct/indirect enhancement of GABA inhibitory effects
  - Reduce activity of glutamate and/or blocking NMDA receptors
  - Binds the α2δ subunit of voltage gated Ca+ channels, inhibit NT release

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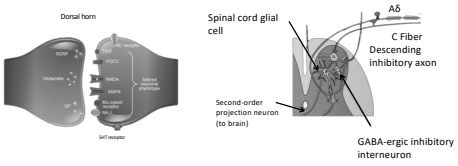
## Site of Action—Antiepileptics







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## Adjuvant Analgesics: Topicals

*Examples*

- Lidocaine patch 5% , eutectic, mixture of lidocaine and prilocaine
- Capsaicin cream/patch
- Diclofenac (cream/liquid/gel/patch)

*Mechanism of action*

- Block sodium channels and inhibit generation of abnormal impulses by damaged nerves
- Depletion of peripheral small fibers and therefore substance P release from sensory nerve endings
- Target local inflammatory response

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## Muscle Relaxants

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

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## Muscle Relaxants—Spasmolytics

- 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 (barbiturate like effects), tizanidine (α-2 agonist), baclofen (GABA agonist), orphenadrine (diphenhydramine/antihistamine)
- Common adverse effects
  - Sedation, lethargy & confusion (cyclobenzaprine), dependence (carisoprodol)

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## Case Study

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

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## Importance for Understanding Pain Mechanisms

- 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 nonpharmacologic 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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