PAINWEEK

Pain Pathways Made Simple

David M Glick, DC, DAAPM, CPE

Disclosures

- Nothing to Disclose

PAINWEEK

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

PAINWEEK

Classification of Pain

- Good pain vs bad pain

Clinical Pearl

PAINweek

Good Pain

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

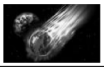
PAINweek

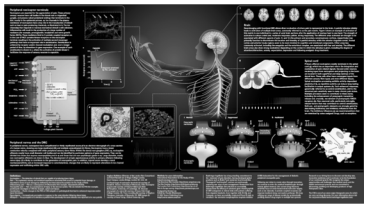
Bad Pain

- **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

PAINweek

Pain Mechanisms

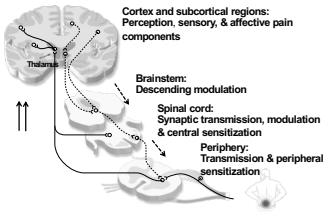




PAINweek

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

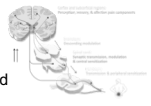
Periphery:
Transmission & peripheral sensitization

PAINweek

- 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

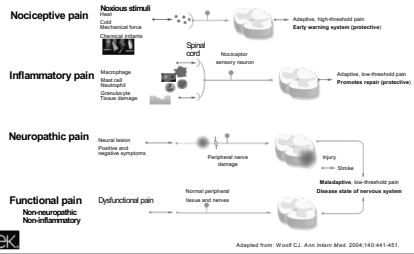
- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (ie, occurring in real time)
- Adapts or changes in response to function—"neuroplasticity"



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

PAINweek

Common Types of Pain

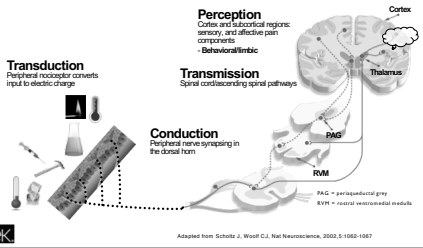


Adapted from: Woolf CJ. *Ann Intern Med.* 2004;140:441-451.

Nociceptive vs Neuropathic Pain

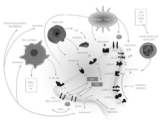
1. Portenoy RK, Kanner RM. In: Portenoy RK, et al, eds. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis Company;1996:4.
2. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: McGraw-Hill Companies Inc; 2000:8-9.

Pain Pathway Steps



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

Transduction: Processing at Peripheral Nerve Endings

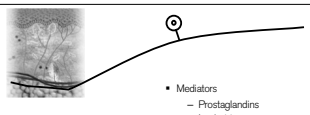


- Conversion of mechanical, thermal or chemical stimuli into an electric charge
- Involves
  - Receptors activated directly by stimuli
  - Injury/inflammatory response

PAINweek

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?

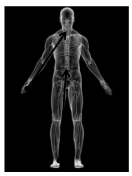


- Nociception
  - Mechanical
  - Thermal
  - Chemical
- Mediators
  - Prostaglandins
  - Leukotrienes
  - Substance P
  - Histamine
  - Bradykinin
  - Serotonin
  - Hydroxyacids
  - Reactive oxygen species
  - Inflammatory cytokines and chemokines

PAINweek

Conduction

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



PAINweek

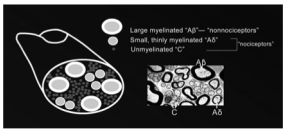
Primary Nociception

- 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

PAINweek

Peripheral Pain Nociceptors

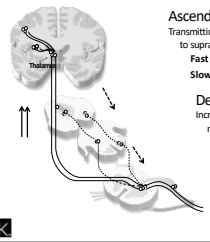


Aβ—muscle spindle secondary endings, touch, and kinesthesia
Aδ—pain, temperature, crude touch, and pressure

PAINweek

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



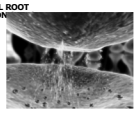
Ascending nociceptive pathways
Transmitting nociceptive impulses from the dorsal horn to supraspinal targets
Fast *(green)* neospinalthalamic
Slow *(yellow)* paleospinalthalamic

Descending inhibitory tracts *(blue)*
Increase or decrease volume control of incoming nociceptive signals reaching the brain
5-HT—serotonin
NE—norepinephrine

PAINweek

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
  - α_2 agonists

PAINWEEK

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

PAINWEEK

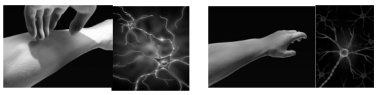
How Acute Pain Becomes Chronic

- 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

PAINWEEK

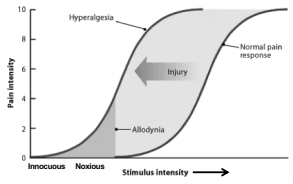
Definitions

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



PAINweek

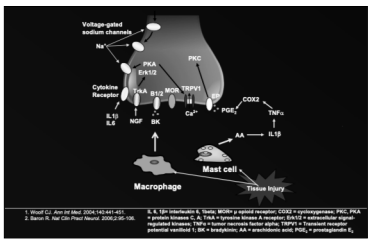
Neuroplasticity in Pain Processing



PAINweek

1. Woolf CJ, Salter MW. Science. 2000;288:1765-1769.
2. Ramsden RI, Howell TW. The perception of pain. In: Kandel ER, Schwartz JH, et al, eds. Principles of Neural Science. 4th ed. New York, NY: McGraw-Hill; 2000:475.
3. Cervero F. Lancet Infect Dis. Pain. 1998;68:13-23.

Neuroplasticity in Peripheral Pain Transmission

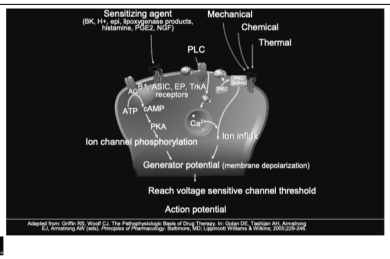


1. Woolf CJ. Ann Int Med. 2004;140:441-451.
2. Baron R. Nat Clin Pract Neurol. 2006;2:95-106.

IL 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

PAINweek

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

PAINWEEK

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

PAINWEEK

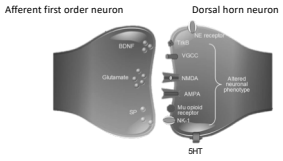
Definitions

- 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.

PAINWEEK

Central Sensitization

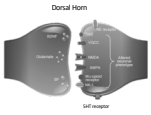


NK-1 = neurokinin 1 receptor; AMPA = alpha-amino-3-hydroxy-5-methyle 4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartic acid; VGCC = voltage gated sodium channel;
TrkB = tropomyosin receptor kinase B; BDNF = brain derived neurotrophic factor; SP = substance P

PAINweek

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

Central Sensitization



Key influences upon signal propagation

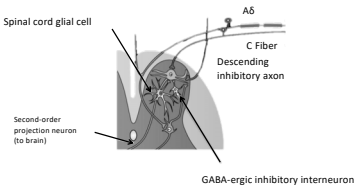
- Excitatory neurotransmitters
  - Substance P, CGRP, glutamate
- NMDA channel activity
  - Glutamate binding
  - Altering channel activity
- Descending inhibitory tracts
  - NE/Serotonin (5HT)
- Mu opioid receptor

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

PAINweek

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

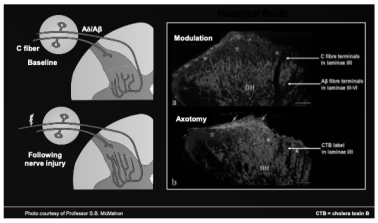
Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing[1,2]



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.

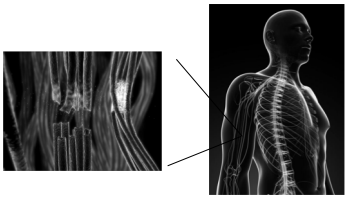
Neuroplasticity: Neural Reorganization



CTB = cholera toxin B

PAINweek

Neuroplasticity: Cross Talk



CTB = cholera toxin B

PAINweek

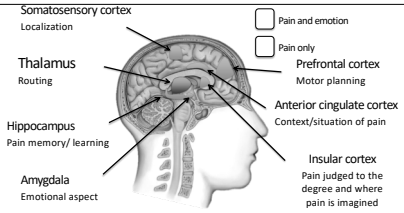
Central Sensitization:
Neuroplasticity in Spinal Cord Processing

- 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]

PAINweek

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.

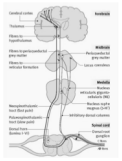
Brain Regions Involved in Pain Processing



PAINWEEK

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

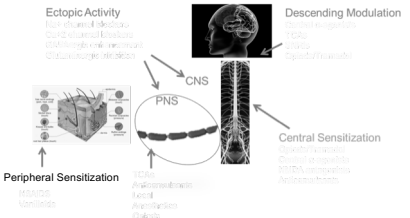
Analgesics that Modify Pain Processes



- Transduction
  - NSAIDs
  - Antihistamines
  - Membrane stabilizing agents
  - Local anesthetic cream
  - Opioids
  - Bradykinin & Serotonin antagonists
- Transmission/modulation
  - Spinal opioids
  - α_2 agonists
  - NMDA receptor antagonists
  - NSAIDs
  - NO inhibitors
  - K^+ channel openers
- Perception
  - Parenteral opioids
  - α_2 agonists
  - General anesthetics
- Conduction
  - Local anesthetics
    - Peripheral nerve, plexus, epidural block

PAINWEEK

Pharmacological Targets in Pain



PAINWEEK

Woolf C, Max M Anesthesiology 2001

The Chronic Pain Armamentarium

Nonopioids
- Acetaminophen
- NSAIDs
- COX-2 inhibitors

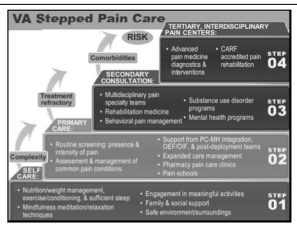
Opioids
- Mu-opioid agonists
- Mixed agonist-antagonists

Adjuvant analgesics
- Antidepressants
- Anticonvulsants
- Topical agents/local anesthetics

PAINWEEK

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

VA DoD Stepped Pain Care Model

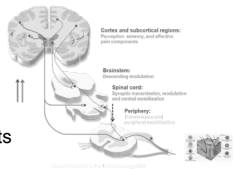


PAINWEEK

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



PAINWEEK

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

PAINweek

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)

PAINweek

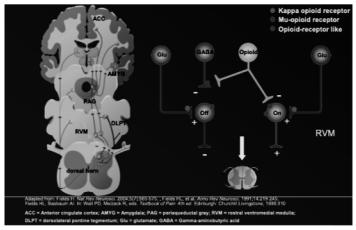
Opioids

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

PAINweek

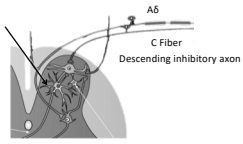
Overview of Descending Pain Inhibitory Pathways and Modulation of Pain Response



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

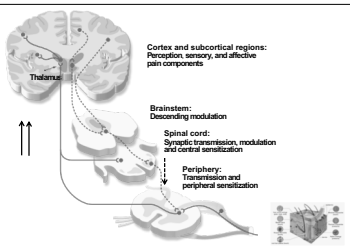
PAINweek

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



PAINweek

Mechanism of Action—Opioids



Adapted from Woolf C, Max M Anesthesiology 2001

PAINweek

Adjuvant Analgesics: Tricyclic Antidepressants

Examples

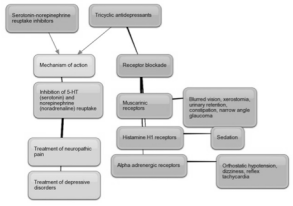
– Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

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)

PAINWEEK

TCAs and SNRIs Pharmacological Properties



PAINWEEK

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!

PAINWEEK

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

PAINWEEK

Serotonin/5-HT Receptors

Family	Type	Mechanism	Potential
5-HT$_1$	G_i/G_o-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_2$	G_q/G_{11}-protein coupled.	Increasing cellular levels of IP$_3$ and DAG.	Excitatory
5-HT$_3$	Ligand-gated Na^+ and K^+ cation channel.	Depolarizing plasma membrane.	Excitatory
5-HT$_4$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_5$	G_i/G_o-protein coupled.[4]	Decreasing cellular levels of cAMP.	Inhibitory
5-HT$_6$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5-HT$_7$	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

PAINWEEK

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

PAINWEEK

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

SNRIs (Serotonin/Noradrenaline Reuptake Inhibitors)

Examples

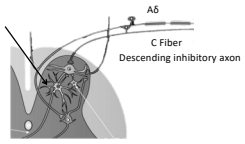
- Duloxetine, milnacipran, and venlafaxine

Mechanism of action

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

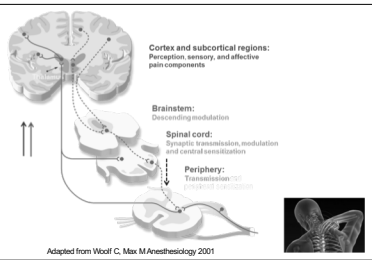
PAINweek

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



PAINweek

Site of Action—SNRIs



PAINweek

Adapted from Woolf C, Max M Anesthesiology 2001

Adjuvant Analgesics: Antiepileptics

Examples

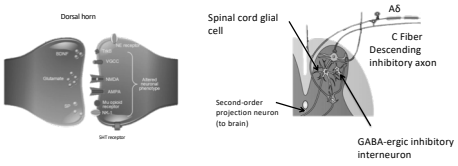
- Gabapentin, pregabalin,* carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine

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

PAINWEEK

Site of Action—Antiepileptics



PAINWEEK

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

PAINWEEK

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

PAINweek

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)

PAINweek

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

PAINweek

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

PAINWEEK