



Pain Pathways Made Simple

David M Glick, DC, DAAPM, CPE

Disclosures

- Nothing to Disclose




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



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

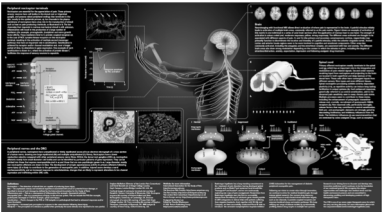
Painweek

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

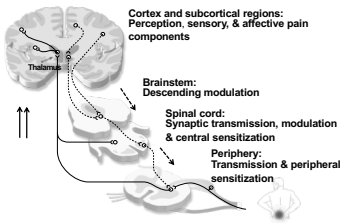
Painweek

Pain Mechanisms



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

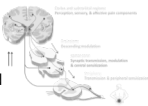
General Anatomy of Pain



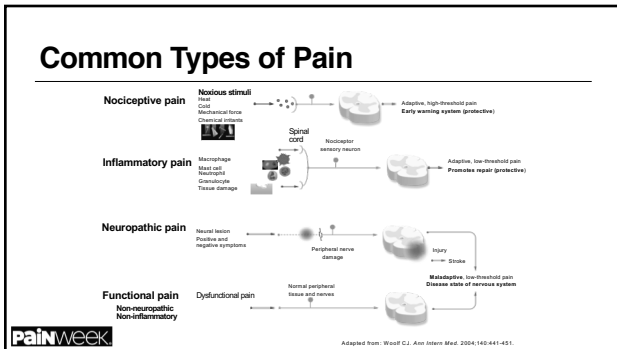
Adapted from Yun-Hahn C.A., Bacon W., Wiesel C.J. Deconstructing the neuroanatomic pain phenotype to reveal neural mechanisms. *Neuron* 90(1): 55-72(4), 03-05-12

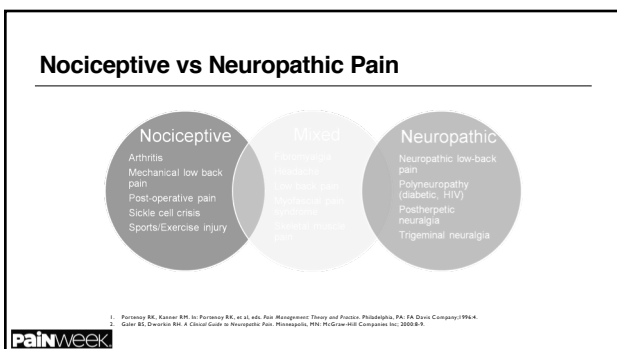
Pain Roadmap: Peripheral and Central Nervous System Landmarks

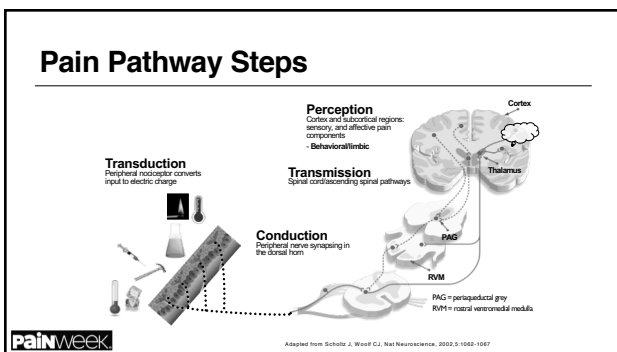
- Physiologic process involving multiple areas of the nervous system
- Bidirectional
- Involves normal as well as pathological processes
- A sensory experience associated with affective and cognitive responses
- Dynamic (ie, occurring in real time)
- Adapts or changes in response to function—"neuroplasticity"




© Garland Science, 2014. In: Kandel E., et al., eds. *Principles of Neural Science*, 5th ed. McGraw-Hill Medical, 2008; chapters 21-23







**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 Daugherty PM, et al. Neurochemistry of nociception and pain processing. In: Bennett G, 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

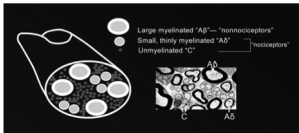
<ul style="list-style-type: none"> ▪ A-delta fibers <ul style="list-style-type: none"> - Small receptive fields - Thermal & mechanical - Myelinated - Rapidly conducting <ul style="list-style-type: none"> • 10-30 m/sec - Large diameter 	<ul style="list-style-type: none"> ▪ C-fibers <ul style="list-style-type: none"> - Broad receptive fields - Polymodal - Unmyelinated - Slower conducting <ul style="list-style-type: none"> • .5-2.0 m/sec - Cross sensitized - Small diameter
---	--





Painweek

Peripheral Pain Nociceptors

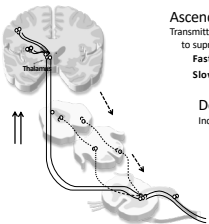


Aβ—muscle spindle secondary endings, touch, and kinesthesia
Aδ—pain, temperature, crude touch, and pressure

Berkman A, Jessell T. The perception of Pain. In Kendal E, Schwartz J. Principles of Neural Science 4th ed. New York, McGraw-Hill, 2000, 852-853.

Painweek

Transmission & Modulation



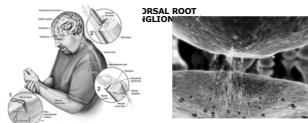
Ascending nociceptive pathways
 Transmitting nociceptive impulses from the dorsal horn to supraspinal targets
Fast (green) neospinothalamic
Slow (yellow) paleospinothalamic

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

Adapted from Yun Hee CA, Basco R, Woolf CJ. Deconstructing the nociceptive pain pathway to reveal neural mechanisms. *Nature* 2012; 485:416-421

Painweek

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



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



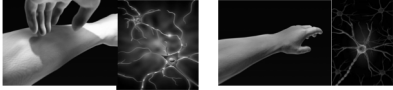
How Acute Pain Becomes Chronic

- **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



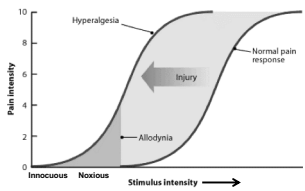
Definitions

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



Painweek

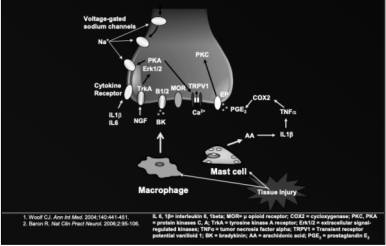
Neuroplasticity in Pain Processing



Painweek

1. Baseler HA, Griffin RW, et al. Pain. 2002;99:117-126.
 2. Baseler HA, Griffin RW. The neurobiology of pain. In: Baseler HA, Schwartz JI, et al, eds. Principles of Neural Science, 4th ed. New York, NY: McGraw-Hill; 2004:117-126.
 3. Cohen J. Curr Biol. 2004;14:1122-1123.

Neuroplasticity in Peripheral Pain Transmission



Painweek

1. Wood CJ. Ann NY Acad Sci. 2004;1024:441-451.
 2. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 3. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 4. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 5. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 6. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 7. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 8. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 9. Baseler HA, Griffin RW. Pain. 2002;99:117-126.
 10. Baseler HA, Griffin RW. Pain. 2002;99:117-126.

Peripheral Sensitization

Released from: Goffo BS, Wood CJ. The Polyphosphoinositide Signaling System. In: Golan DE, Fagan MA, Aronson EJ, Anwarling AM (eds). Principles of Pharmacology, Baltimore, MD: Lippincott Williams & Wilkins, 2008:220-242

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}

Painweek

1. Kandel ER, Schwartz JH, Jessell TM, editors. Principles of Neural Science (Fourth Edition). New York: McGraw Hill (Health Professions Division); 2000:472-481.
 2. Millan MJ. Progress in Neurobiology. 1998;57:1-164.
 3. Dickenson AH. Brit J Anaesth 1995;75:193-200.
 4. Quasthoff and Dickenson. ANS. Neuroreport 2000;11:1817-21.

Central Sensitization

Afferent first order neuron **Dorsal horn neuron**

NMDA = N-methyl-D-aspartate receptor; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate; VGCC = voltage-gated calcium channel; SHT = 5-hydroxytryptamine receptor; CGRP = calcitonin gene-related peptide; SP = substance P

Painweek Adapted from Scholz J, Woolf CJ. *Nat Neurosci*. 2003;5:1063-1067

Central Sensitization

Dorsal Horn

Key influences upon signal propagation

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

Painweek Adapted from Scholz J, Woolf CJ. *Nat Neurosci*. 2003;5:1063-1067

Dorsal Horn of the Spinal Cord Serves as a Relay Station in Pain Processing^{1,2}

Spinal cord glial cell
 Second-order projection neuron (to brain)
 Aδ
 C Fiber
 Descending inhibitory axon
 GABA-ergic inhibitory interneuron

Painweek

 Adapted from: 1. Baron R. Mechanisms of disease: neuropathic pain: a clinical perspective. *Nat Clin Pract Neurol*. 2005;1:55-66. 2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann NY Acad Sci*. 2004;104:1-11.

Neuroplasticity: Neural Reorganization

Photo courtesy of Professor S.S. McMillan

CTB = cholerera toxin B

Painweek

Neuroplasticity: Cross Talk

CTB = cholerera 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⁺/Ca²⁺ (receptor open longer)
 - Modulation—excitatory/inhibitory neurotransmitters
 - Decreased tone—descending inhibitory pathways²
 - Activation/migration of glial cells into the spinal cord³
 - Changes in the thalamus and primary somatosensory cortex⁴

Painweek

1. McMillan S, Woodruff CJ. *Brain*. 2005;128(12):3124-3133. 2. Chubbuck MH, et al. *Ann NY Acad Sci*. 2005;1060:12-24. 3. Wesseler Frank J, et al. *NeuroReport*. 2005;16(15):302-307. 4. Q. Zhang G, et al. *Exp Brain Res*. 1992;92:227-235.

Brain Regions Involved in Pain Processing

Somatosensory cortex
Localization

Thalamus
Routing

Hippocampus
Pain memory/learning

Amygdala
Emotional aspect

Prefrontal cortex
Motor planning

Anterior cingulate cortex
Context/situation of pain

Insular cortex
Pain judged to the degree and where pain is imagined

Legend:
 Pain and emotion
 Pain only

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 agonists
 - NMDA receptor antagonists
 - NSAIDs
 - NO inhibitors
 - K⁺ channel openers
- Perception**
 - Parenteral opioids
 - α agonists
 - General anesthetics
- Conduction**
 - Local anesthetics
 - Peripheral nerve, plexus, epidural block

Painweek

Pharmacological Targets in Pain

Peripheral Sensitization
NSAIDs, Venlafaxine

Ectopic Activity
NSAIDs, Gabapentin, Carbamazepine, Clonidine, Venlafaxine, Amitriptyline

Descending Modulation
Spinal opioids, SSRIs, Serotonin/Tryptophan

Central Sensitization
NSAIDs, Antiepileptics, SSRIs, Anticoagulants, Opioids

CNS
NSAIDs, Antiepileptics, SSRIs, Anticoagulants, Opioids

Painweek

Woolf C. Max M Anesthesiology 2001

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

Legend:
 ● Kappa opioid receptor
 ○ Mu-opioid receptor
 ○ Opioid-receptor like

Adapted from: Fields HL. In: The Pain System. 2004. 307-322. Fields HL, et al. Atlas for Research. 1997. 12-19-2005.
 ACC = Anterior cingulate cortex; 5-HT = 5-hydroxytryptamine; GABA = gamma-aminobutyric acid; RVM = rostral ventromedial medulla; SLPF = serotonergic pain pathway; Glu = glutamate; GABA = gamma-aminobutyric acid.

Painweek

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

A6
 C Fiber
 Descending inhibitory axon

Painweek

Mechanism of Action—Opioids

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

Brainstem:
 Descending modulation

Spinal cord:
 Synaptic transmission, modulation and central sensitization

Periphery:
 Transmission and peripheral sensitization

Adapted from Woolf C, Max M. Anesthesiology 2001

Painweek

Adjuvant Analgesics: Tricyclic Antidepressants

Examples

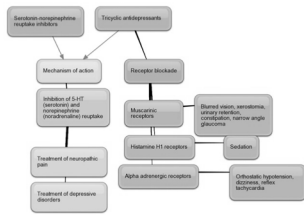
- Amitriptyline, desipramine, doxepin, imipramine, nortriptyline

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)



TCA's and SNRIs Pharmacological Properties



<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!



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 (**GPCBs**) 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 ₁₂ -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-HT_{1a} (blood ves/CNS)
 - Addiction
 - Aggression
 - Anxiety
 - Appetite
 - BP
 - Cardiovascular function
 - Emesis
 - Heart rate
 - Impulsivity
 - Memory
 - Mood
 - Nausea
 - Nociception
 - Penile erection
 - Pupil dilatation
- 5-HT_{1a} (*cont'd*)
 - Respiration
 - Sexual behavior
 - Sleep
 - Sociability
 - Thermoregulation
- 5-HT_{5a} & 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

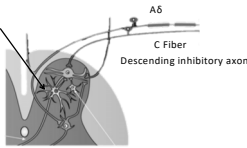
- Duloxetine, milnacipran, and venlafaxine

Mechanism of action

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

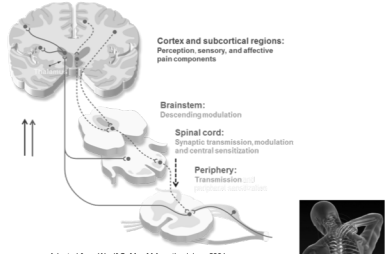
PainWeek

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



PainWeek

Site of Action—SNRIs



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

Brainstem:
Descending modulation

Spinal cord:
Synaptic transmission, modulation and central sensitization

Periphery:
Transmission and modulation

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 $\alpha 2\delta$ subunit of voltage gated Ca+ channels, inhibit NT release

PainWeek

Site of Action—Antiepileptics

The diagram illustrates the spinal cord's dorsal horn and associated neural pathways. Key components labeled include the dorsal horn, spinal cord glial cell, second-order projection neuron (to brain), GABA-ergic inhibitory interneuron, A δ fibers, and C fibers with descending inhibitory axons.

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