PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

PALLIATIVE CARE

Pain Pathogenesis

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Titles and Affiliations

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Online Graduate Studies in Palliative Care (PhD, Master of Science, Graduate Certificates), University of Maryland Baltimore

Disclosures

Learning Objectives

1. List the components of pain signaling
2. Describe the role of A-delta and C-fibers in pain signaling
3. Define concepts of currently accepted models
4. Given a patient case, differentiate between visceral, somatic, and neuropathic pain

Why should we care?

- 100 million Americans suffer from pain daily
- Incidence higher than the combination of
  - Diabetes (25.8 million)
  - Coronary heart disease (16.3 million)
  - Stroke (7 million)
  - Cancer (11.9 million)
- Inadequate treatment of acute pain can lead to chronic pain
- Chronic pain can result in long-term disability

IOM (Institute of Medicine). 2011. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press.

Consequences of untreated pain

- Functional disability
- Changes in mood and appetite
- Stress and fatigue
- Decreased sleep
- Immunity effect
- Decreased quality of life
- Reduced ability to perform ADLs

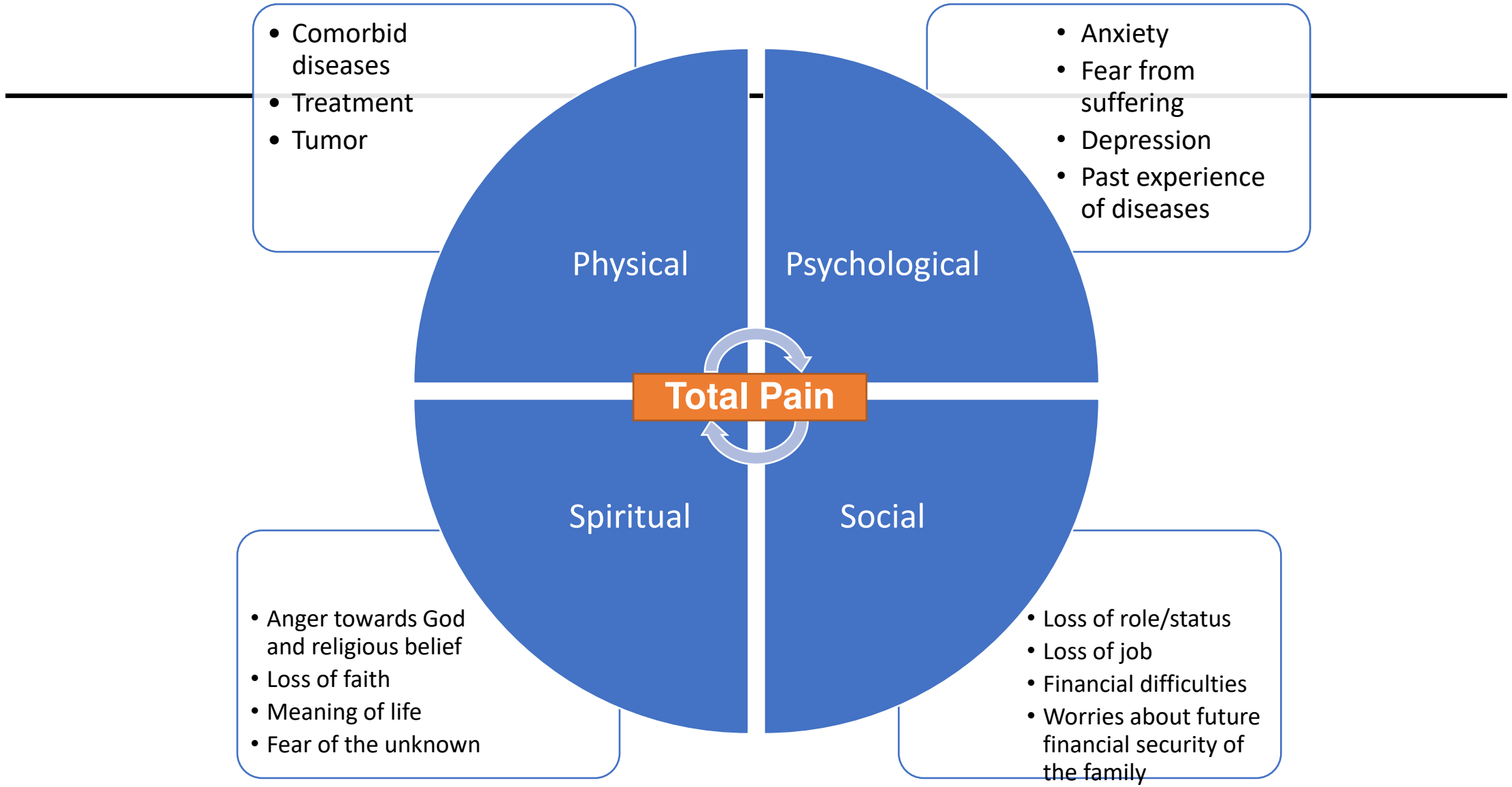
Pain is….

- Objective
- Only physical
- Normal part of aging
- Improves character
- Only treated if severe
- A combination of the awareness of painful stimuli and the emotional impact of the experience

What is Pain?

- "Unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage" – IASP
- "…whatever the experiencing person says it is, existing whenever and wherever the person says it does" – Margo McCaffery
- Concept of "total pain" – Cicely Saunders

Raja. *PAIN.* 2020;161(9):1976-1982. Pasero. *Am J Nurs*. 2018;118(3):17. Ong. *BMJ*. 2005;331(7516):576. www.iasp-pain.org/resources/terminology/.



Ong. *BMJ*. 2005;331(7516):576.

Descriptions of Pain

Intensity

- Mild, moderate, severe

Time course

- Acute vs chronic
- Baseline vs breakthrough

Classification

- Nociceptive
- Neuropathic

Nociceptive Pain

Nociceptors

- Sensory receptors throughout the body
  - Skin
  - Internal organs
  - Muscle
  - Joints and tendons
- Respond to harmful stimuli in the periphery
  - Thermal
  - Chemical
  - Mechanical
  - Proprioceptive

Dubin. *J Clin Invest*. 2010;120(11):3760-3772.

Nociceptive Pain

- Activated by noxious stimuli
- Warning of actual or potential tissue damage
- Protective mechanism!
- Types:
  - Visceral pain – Arises from internal organs; diffuse, difficult to pinpoint
  - Somatic pain – Musculoskeletal, well localized

Dubin. *J Clin Invest*. 2010;120(11):3760-3772.

The Pain Pathway

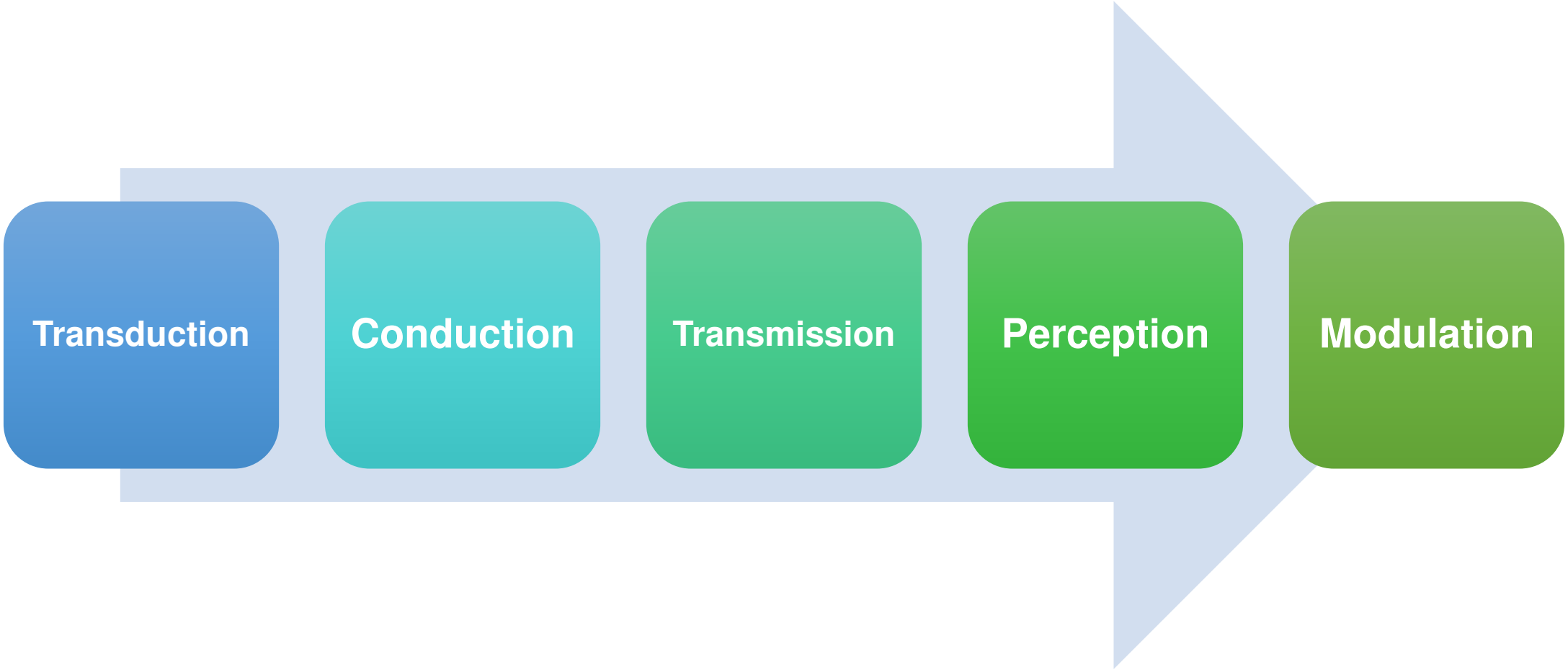
- Ascending pathway
  - Signal travels along complex neural network via afferent neurons
    - A-delta fibers
    - C-fibers

	A-delta fibers	A-beta fibers	C-fibers
Diameter	Small (2-5 mcm)	Large	Small (<2 mcm)
Myelination	Myelinated	Myelinated	Unmyelinated
Conduction velocity	Fast (>40 m/sec)	Slow (5-30 m/sec)	Slowest (<2 m/sec)
Activation threshold	High and low	Low	High
Sensation	Rapid, sharp, localized pain	Light touch, non-noxious stimuli	Slow, diffuse, dull pain

  - Peripheral signal → central interpretation

www.practicalpainmanagement.com/resources/diagnostic-tests/conceptual-model-pain-measurement-diagnosis?page=0,1.

Pain Processing Pathway



Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior. Anatomy and physiology of pain. In: *Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives*. 1987:chapter 7.

1. Transduction

- Injury from a thermal, chemical, or mechanical stimuli activates peripheral endings of sensory neurons (nociceptors)
- Nociceptors translate (transduce) a physical stimulus into an electrical signal (also called an action potential)
- Depolarization of afferent neuron is triggered by "inflammatory soup"
  - Bradykinin, H^+, histamine, prostaglandins, leukotrienes, substance P, neurokinin A, serotonin

McEntire. *Expert Rev Clin Pharmacol*. 2016;9(8):1069-1080.
Fei Yam. *Int J Mol Sci*. 2018;19(8):2164.

2. Conduction

- Pain signal sent from dorsal horn of spinal cord to thalamus along the spinothalamic tract (STT)
  - First carried by A-delta fibers
  - Then carried by slower C-fibers
- STT divides before reaching the thalamus
  - Lateral STT – sensory and discriminatory pain perception
  - Medial STT – affective and motivational pain perception
- Signal moves from thalamus along sensory tracts to the brain
  - Somatosensory area – sensory aspects of pain
  - Frontal cortex and limbic system – emotional response to pain

Yen. *Acta Anaesthesiologica Taiwanica*. 2013;51(2):73-80.

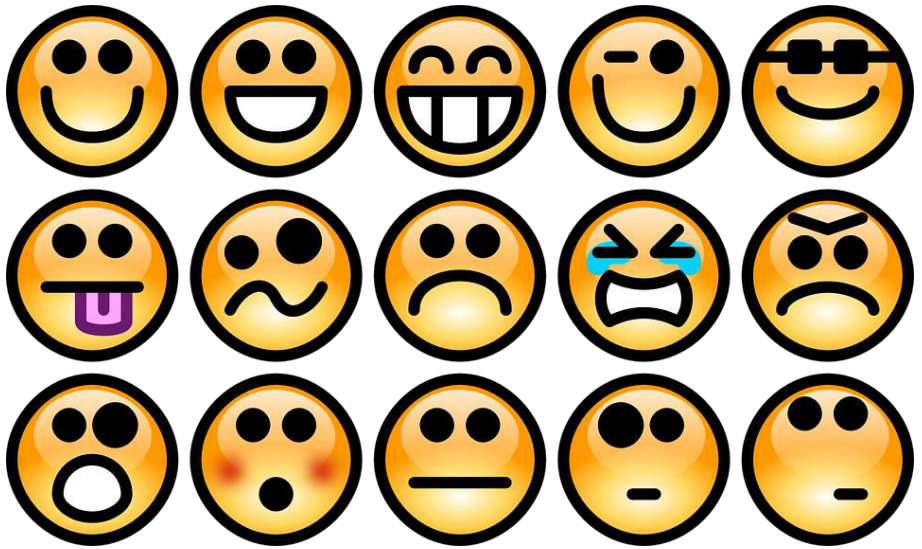
3. Transmission

- Message from primary afferent neuron passed on to second-order projection neurons in the dorsal horn
- Mediated by:
  - Pre-synaptic voltage-gated calcium channel
  - Excitatory signaling by glutamate at post-synaptic NMDA receptors
- Occurs at 3 major junctions:
  - Nociceptor and dorsal horn of the spinal cord
  - Spinal cord and thalamus and brainstem
  - Thalamus into the cerebral cortex

Urch. *Rev Pain*. 2007;1(1):2-6.

4. Perception

- Pain signal ultimately enters the brain through the thalamus
- Signals are routed to regions of the brain involved with sensation, autonomic nervous system, motor response, emotion, stress, behavior
- Subjective experience of pain
  - May be influenced by:
    - Age
    - Gender
    - Stress
    - Memory



Apkarian. *Curr Opin Neurobiol*. 2008;18(4):464-468.

5. Modulation

- Dampening or amplification of nociceptive signal
  - Variation between activation of the receptor and resulting sensory experience of pain
- Primarily in ascending tract
  - High concentrations of mu, kappa, and delta opioid receptors in dorsal horn of spinal cord

Budai. *J Neurophysiol*. 1998;79(2):677-687.

5. Modulation

- Descending pathway
  - Axons travel from somatosensory cortex and hypothalamus to spinal cord, inhibit ascending signals
  - Involves variety of modulating substances
    - Endogenous opioids
      - Endorphins, enkephalins, dynorphins, endomorphins
    - Serotonin
    - Norepinephrine
    - Inhibitory GABA signaling
  - Activated by systemic or spinal opioid injection, electrical stimulation, stress, suggestion, and pain

Dougherty. Chapter 4: Somatosensory Pathways. Neuroscience Online: nba.uth.tmc.edu/neuroscience/m/s2/chapter04.html.
Kirkpatrick. *Clin Transl Sci*. 2015;8(6):848-856.

5. Modulation

- US Army physician during WWII, H.K. Beecher
  - Observed remarkable dampening of pain experienced by soldiers
  - Three-quarters of badly wounded soldiers reported no pain to moderate pain and did not want pain medications
    - Compound fractures of long bones
    - Penetrating wounds of abdomen, thorax, cranium

5. Modulation

- **Gate Control Theory**
  - Proposed by Melzack and Wall in 1965
  - Gating mechanism within dorsal horn that integrates ascending and descending pathways
  - Nonpainful stimuli (rubbing an injured area) closes the gate to painful stimuli and prevents it from passing on to CNS
  - Can be manipulated by medications, transduction, transmission, modulation, and psychosocial interventions

Self-Assessment!

- The process of converting physical stimuli into an electrical stimulus is _____.

  A. Transduction
  B. Conduction
  C. Transmission
  D. Perception

Self-Assessment!

- The process of converting physical stimuli into an electrical stimulus is _____.

A. Transduction
B. Conduction
C. Transmission
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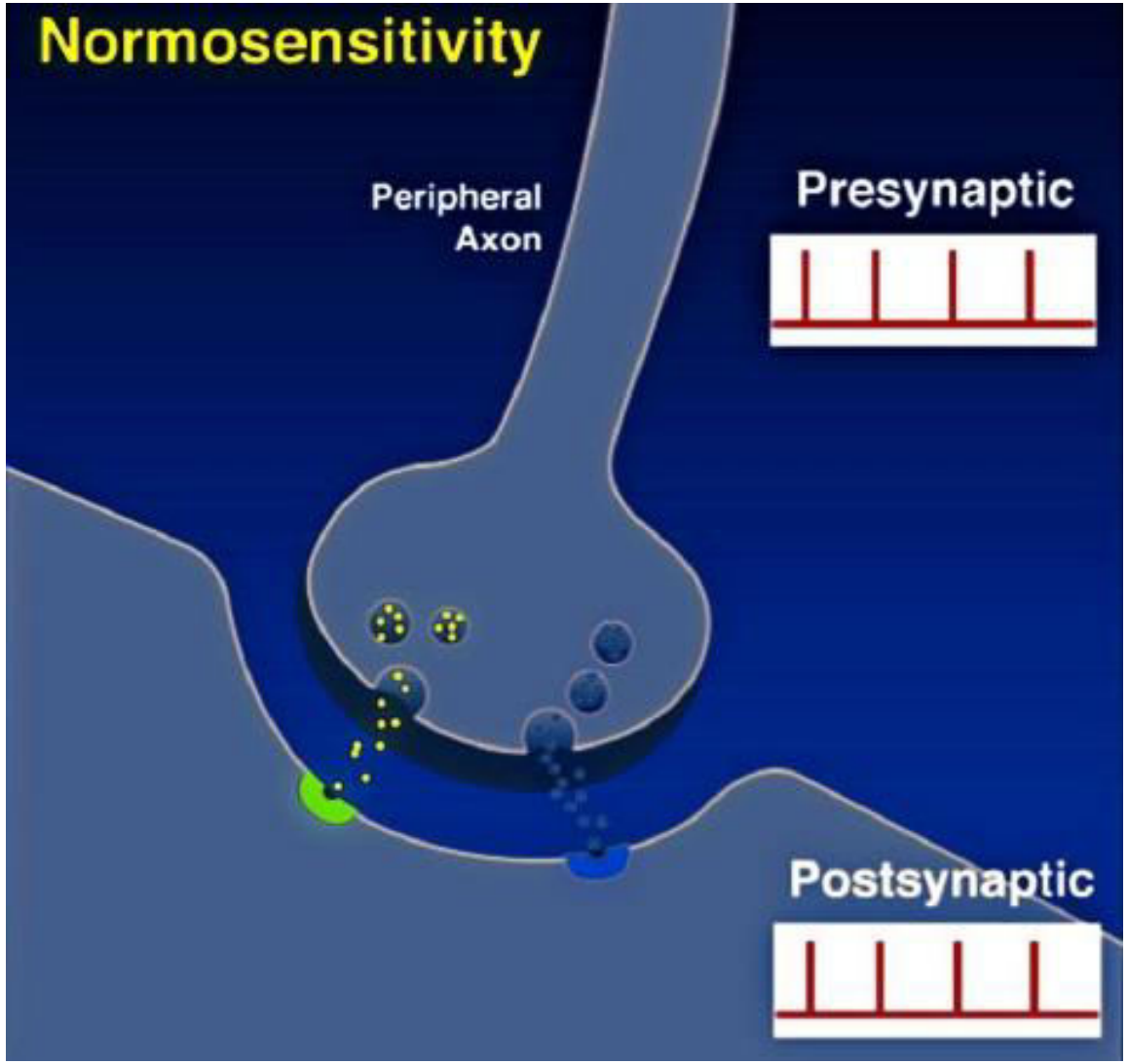
Normal Signaling

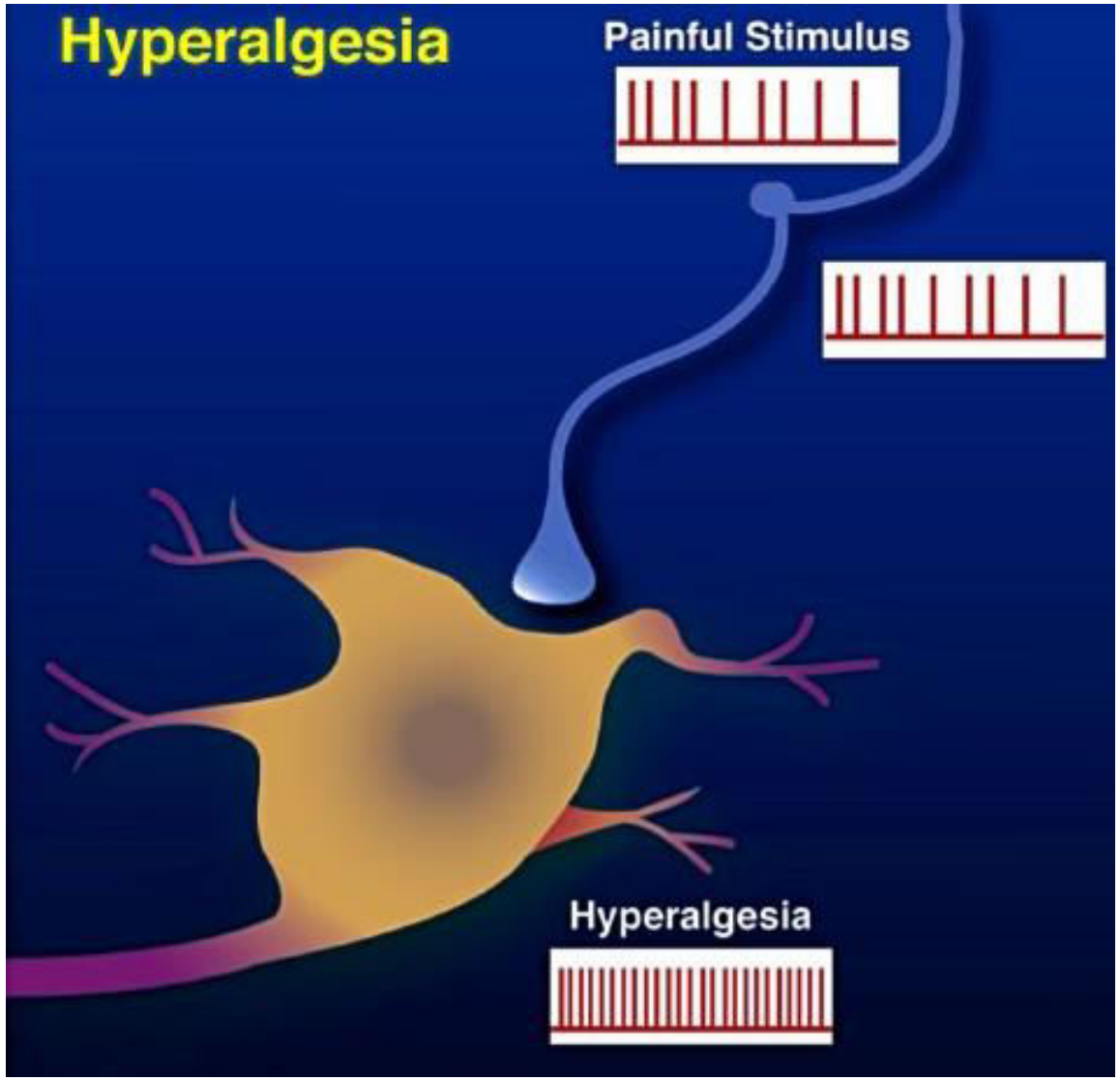
- Postsynaptic action potentials are equivalent to presynaptic potentials



www.practicalpainmanagement.com/pain/demystifying-pain-pathways; used with permission.

Hyperalgesia

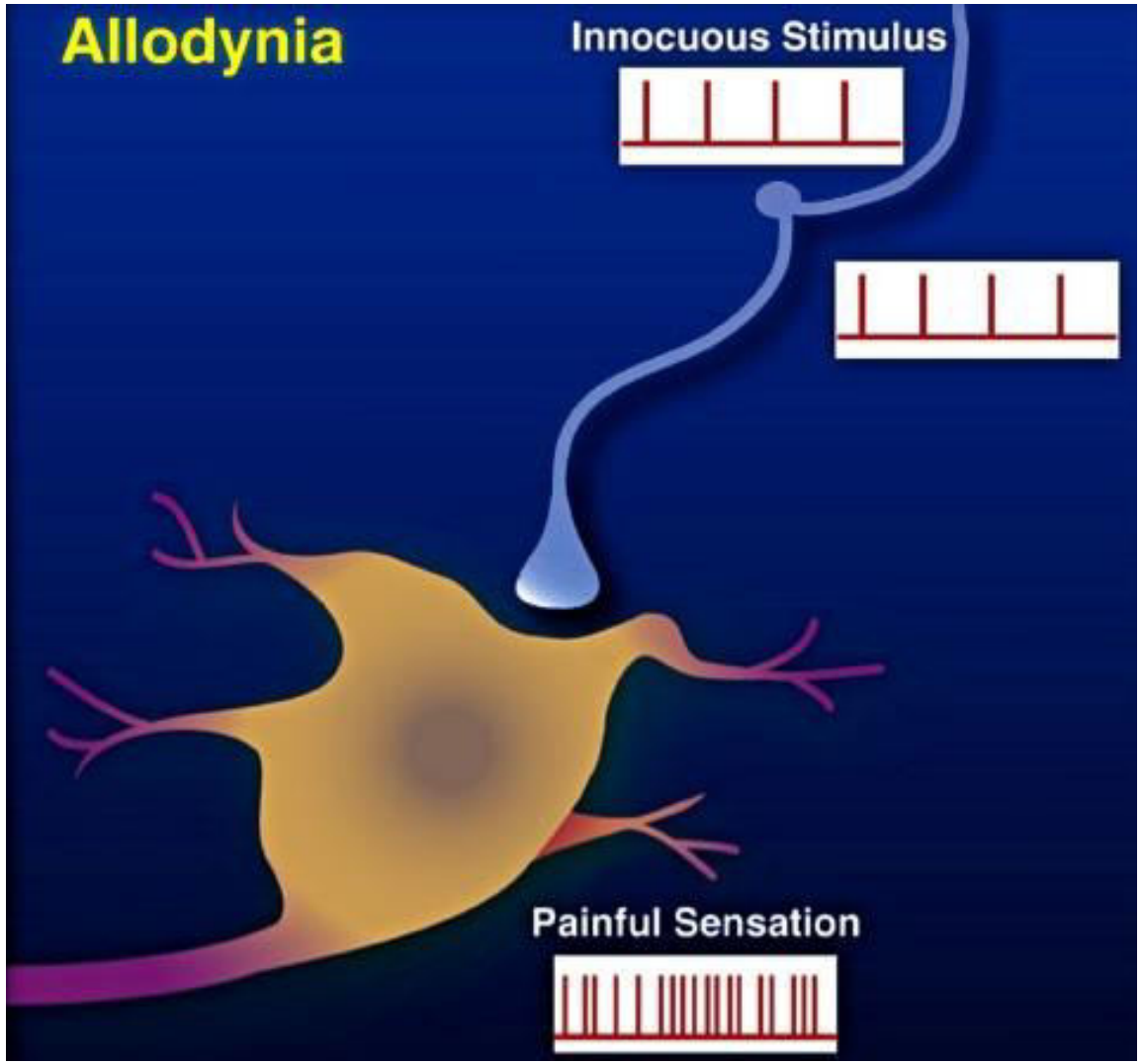
- Amplification of painful response relative to the stimuli



www.practicalpainmanagement.com/pain/demystifying-pain-pathways; used with permission.

Allodynia

- Nonpainful stimuli perceived as painful



www.practicalpainmanagement.com/pain/demystifying-pain-pathways; used with permission.

Sensitization

- Stimuli triggers more intense and prolonged painful response
- Heightened sensitivity in adjacent areas
- Not necessarily associated with damage to the neurons
- May involve peripheral sensitization, central sensitization, or both
- Increased prevalence in chronic pain syndromes

Swift. *Nursing Times*. 2018;114:22-26.

Sensitization

- Mediated by:
  - Voltage-gated sodium channels
  - Biochemical mediators
    - Substance P
    - Serotonin
    - Histamine
    - Acetylcholine
    - Bradykinin

Bennett. *Physiol Rev*. 2019;99(2):1079-1151.

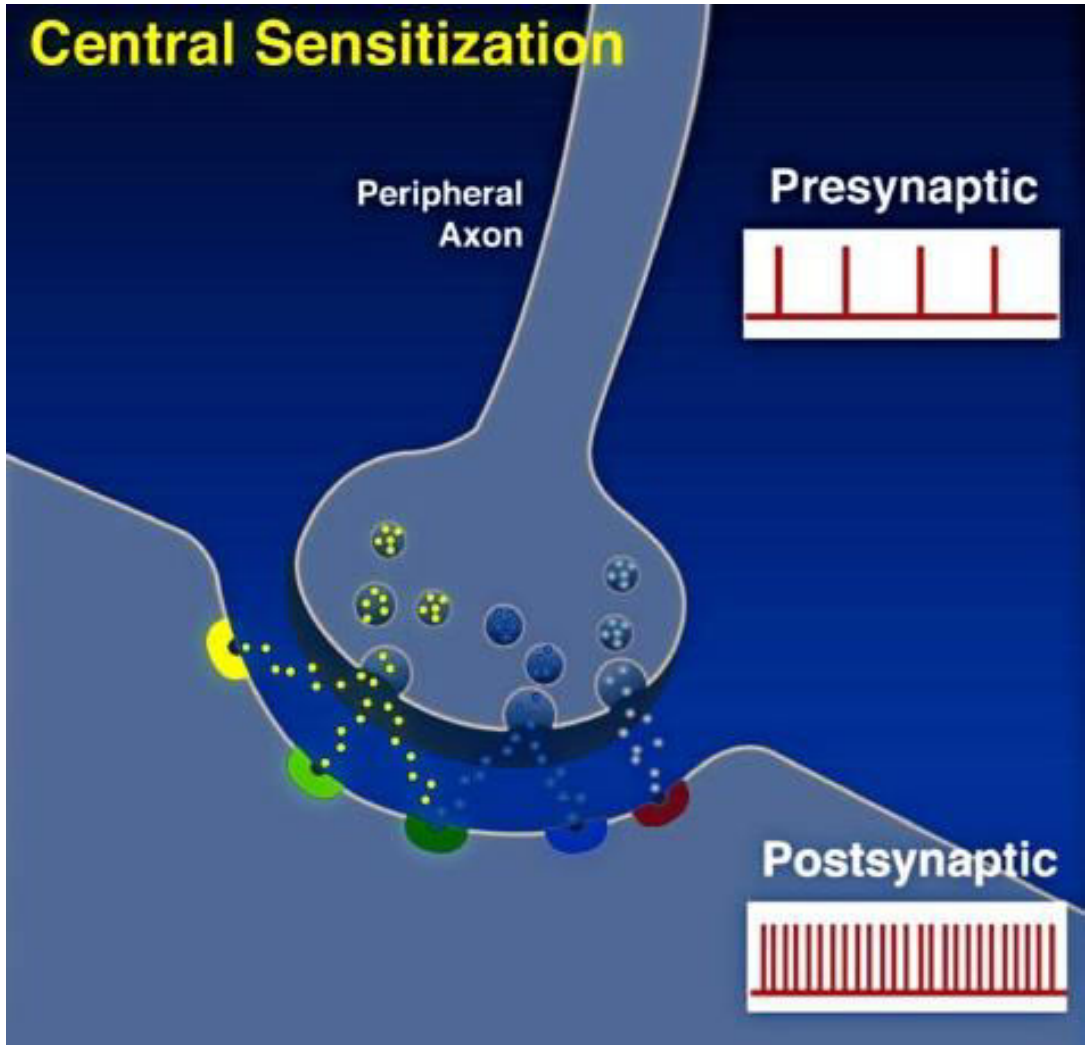
Peripheral Sensitization

- Nociceptor threshold is lowered
  - Painful response to nonpainful stimuli
  - Magnification of painful stimuli transmitted

He. *StatPearls.* www.ncbi.nlm.nih.gov/books/NBK537129/.

Central Sensitization

- Central neuronal threshold is lowered
- Amplification of stimulus



www.practicalpainmanagement.com/pain/demystifying-pain-pathways; used with permission.

Central Sensitization Characteristics

Spontaneous activity

Reduced activation threshold for peripheral stimuli

Increased response to suprathreshold stimuli

Enlarged receptive field

Pathologic pain

- Neuropathic, inflammatory, migraine, IBS, fibromyalgia

Latremoliere. *J Pain.* 2009;19(9):895-926.

Peripheral vs Central Sensitization

Peripheral Sensitization

- Altered heat sensitivity
- Restricted to site of tissue injury
- Temporary
- Protective

Central Sensitization

- Altered mechanical sensitivity
- Secondary hyperalgesia
- Long-term, permanent
- Pathologic
- Neurons previously responsive only to noxious stimuli now respond to both noxious and innocuous stimuli
- Temporal windup

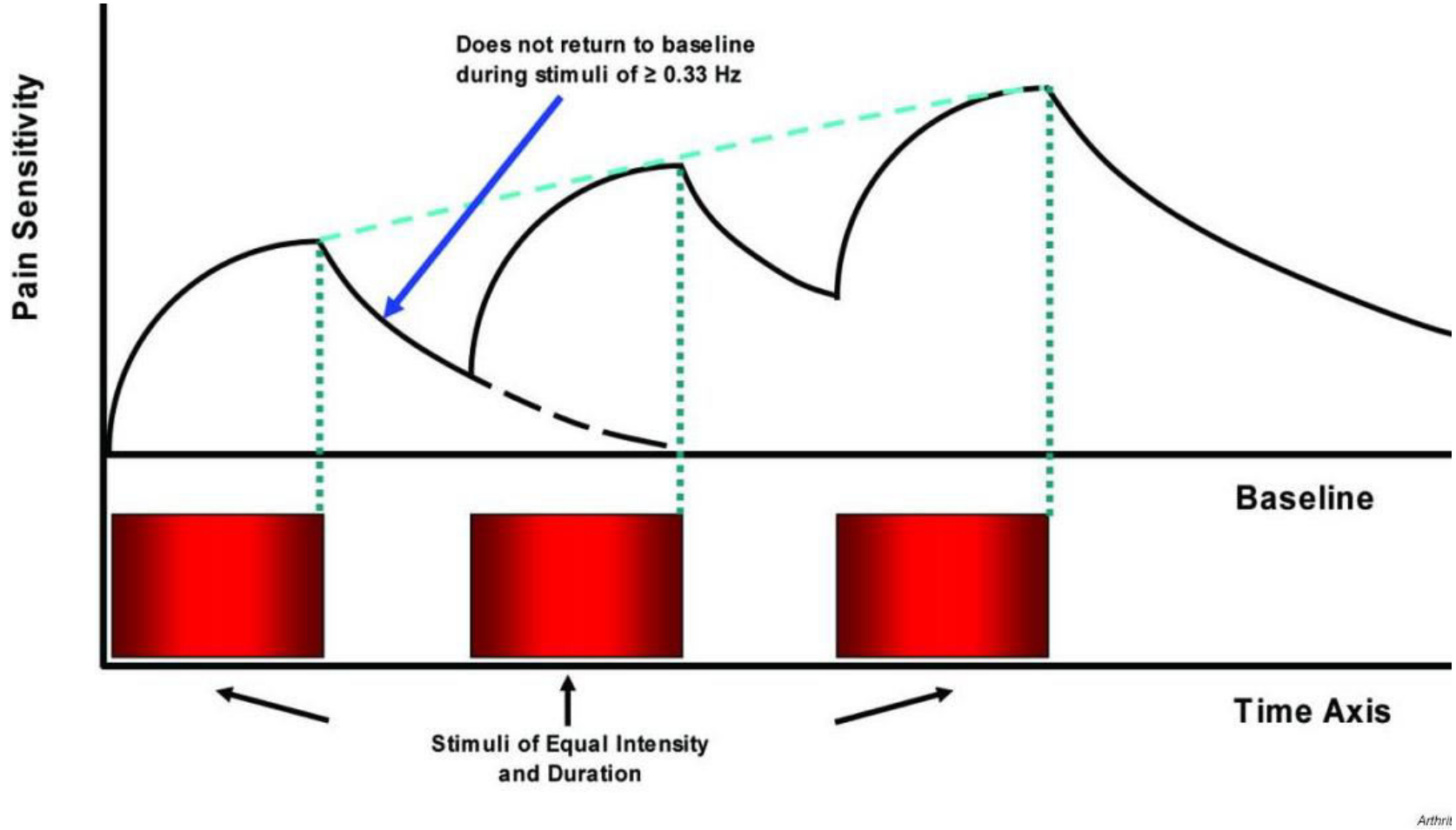
Latremoliere. *J Pain.* 2009;19(9):895-926.

Wind-Up

- Frequency-dependent increase in spinal cord neuron excitability
- Response to barrage of nociceptive impulses
- Triggered by stimulation of afferent C-fibers
- Mediated by:
  - Glutamate (NMDA) receptors
  - Tachykinin receptors
  - Potassium channels
  - Calcium channels

Herrero. *Prog Neurobiol*. 2000;61(2):169-203.

Wind-Up

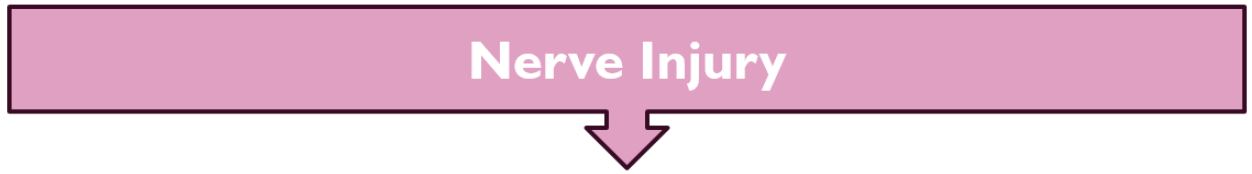


www.arthritis-research.com/content/figures/ar1950-1-l.jpg.

Neuropathic Pain

Neuropathic Pain

- Damage to or dysfunction of peripheral or central nerves
  - May be direct or secondary to damage to non-neuronal tissue
  - Lesion may occur at any point



- Post-herpetic neuralgia
- HIV
- Diabetes
- Trauma
- Multiple sclerosis
- Metabolic abnormalities
- Malignancy
- Drugs!

my.clevelandclinic.org/health/diseases/15833-neuropathic-pain.

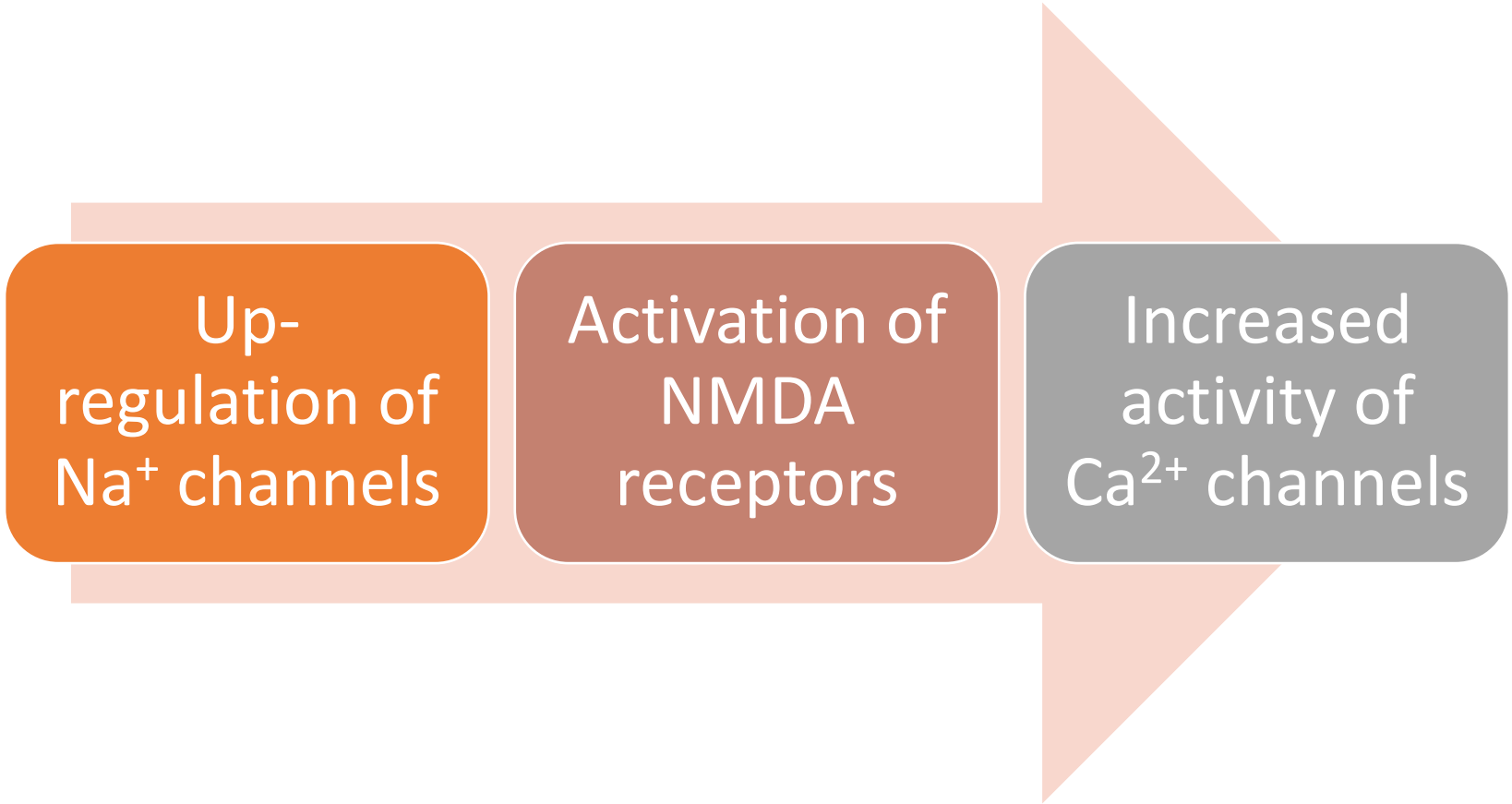
Clinical Presentation

- Spontaneous pain
- Paresthesia and dysesthesia
- Causalgia
- Paroxysmal pain
- Hyperalgesia
- Allodynia

Neuropathic Pain

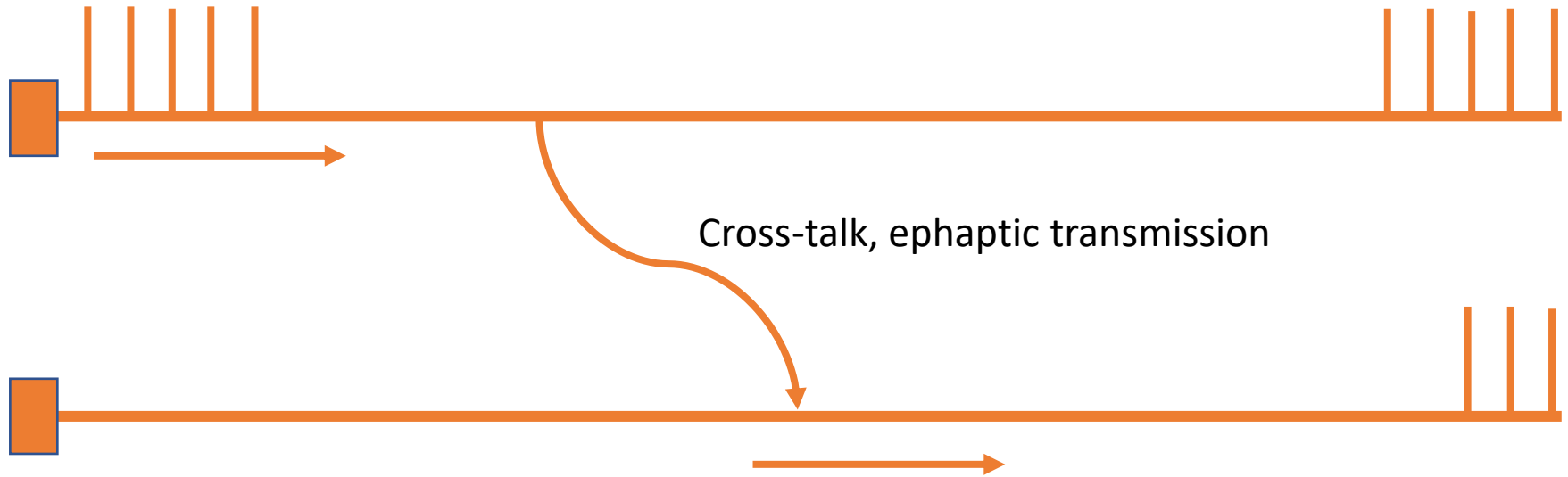
- Pathophysiology is complex, may involve combination of mechanisms
- Significant variation between syndromes
  - Demyelination
  - Mitochondrial toxicity
  - Glial cell activation
  - Ion channel involvement
  - Damage to inhibitory, descending pathways
- May be stimulus dependent or independent

Neuropathic Pain Pathophysiology



Neuropathic Pain

- Cross-talk
  - Development of atypical connections between demyelinated nerves at sites of damage



Adapted from: Nix W. (2017) Pain mechanics. In: Muscles, Nerves, and Pain. Springer, Berlin, Heidelberg.

Self-Assessment!

- Which of the following does NOT play a critical role in the pathogenesis of neuropathic pain?
  - A. NMDA receptors
  - B. Calcium channels
  - C. Up-regulation of voltage-gated sodium channels
  - D. AMPA receptors

Self-Assessment!

- Which of the following does NOT play a critical role in the pathogenesis of neuropathic pain?
  - A. NMDA receptors
  - B. Calcium channels
  - C. Up-regulation of voltage-gated sodium channels
  - D. AMPA receptors

Treatment Strategies

Transduction

- Capsaicin

Inflammation

- NSAIDs

Conduction

- Lidocaine, TCAs, SNRIs

Transmission

- Opioids, ketamine, methadone, TCAs, gabapentinoids, SNRIs

Perception

- Nonpharmacologic therapies

Modulation

- Nonpharmacologic therapies, TCAs, opioids, cannabinoids

Summary

- Pain is a complex, multidimensional phenomenon
- Numerous pathways with numerous targets for intervention
- Not limited to a physical experience

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