Pain is Pain: Acute and Chronic

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Objectives

- Participants will understand the basic pain processes.
- Participants will be able to differentiate the different pain terminologies.
- Participants will understand basic tool and treatments for chronic pain patients.

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Disclosure

- I have no financial disclosure or conflicts of interest with the presented material in this presentation.

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an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

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What is pain?

- Most common reason a patient sees a health care provider
- Different ways to classify pain
  - Length
    - Acute- primarily due to nociception
    - Chronic- Neuropathic, physiological and behavioral factors
  - Physiology
    - Nociceptive or neuropathic
  - Etiology
    - Arthritis or cancer pain
    - Physiologic or Pathologic
  - Affected area
    - Headache or lower back pain

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Four Major Processes of Pain

- Transduction
- Transmission
- Modulation
- Perception

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Transduction

Transduction	Injured tissues release a variety of chemicals that activate peripheral nerves and/or cause immune cells to release proinflammatory compounds. The peripheral nerves transduce this chemical soup into an action potential, so that the extent of tissue injury can ultimately be interpreted by the brain. • A-delta fibers transmit "fast pain" that is sharp and well localized • C-fibers transmit "slow pain" that is dull and poorly localized Inflammation also contributes to: • Reduced threshold to pain stimulus (allodynia) • Increased response to pain stimulus (hyperalgesia)

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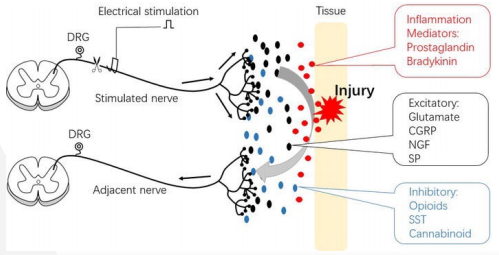
Transduction



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Substance P	Neurokinin–1	Excitatory
Calcitonin gene-related peptide		Excitatory
Glutamate	NMDA, AMPA, kainate, quisqualate	Excitatory
Aspartate	NMDA, AMPA, kainate, quisqualate	Excitatory
Adenosine triphosphate (ATP)	P_1, P_2	Excitatory
Somatostatin		Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	μ, δ, κ	Inhibitory
β-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α_2	Inhibitory
Adenosine	A_1	Inhibitory
Serotonin	5-HT_1 (5-HT_{1A})	Inhibitory
γ-Aminobutyric acid (GABA)	A, B	Inhibitory

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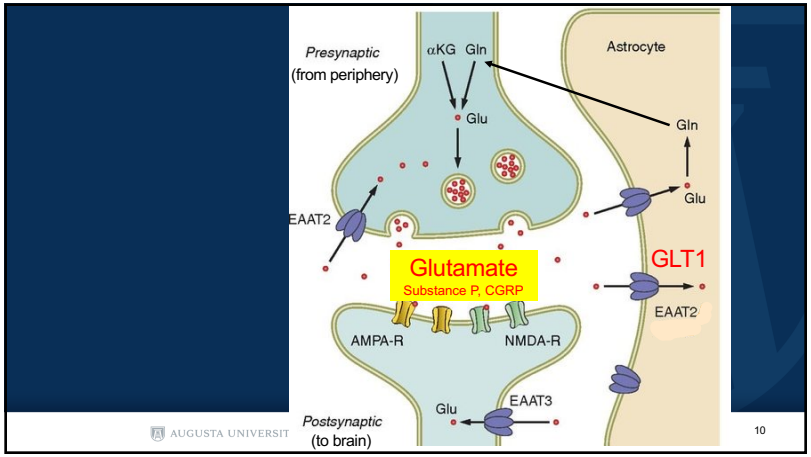

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Transmission

Transmission	The pain signal is relayed through the three-neuron afferent pain pathway along the spinothalamic tract • First-order neuron: periphery to dorsal horn (cell body in dorsal root ganglion) • Second-order neuron: dorsal horn to thalamus (cell body in dorsal horn) • Third-order neuron: thalamus to cerebral cortex (cell body in thalamus)

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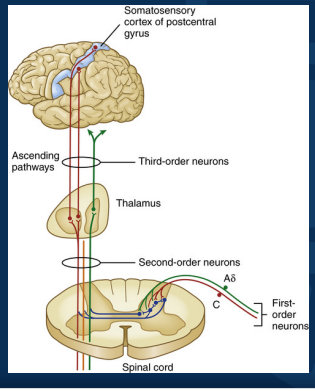

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Modulation

Modulation	The pain signal is modified (inhibited or augmented) as it advances towards the cerebral cortex The most important site of modulation is the substantia gelatinosa in the dorsal horn (Rexed lamina II and III) • The descending inhibitory pain pathway begins in the periaqueductal gray and the rostroventral medulla. It projects to the substantia gelatinosa. Pain is inhibited when: 1. Spinal neurons release GABA and glycine (inhibitor neurotransmitters) 2. The descending pain pathway releases NE, 5-HT, and endorphins Pain is augmented by: 1. Central sensitization 2. Wind-up

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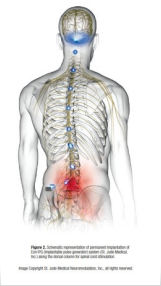
Modulation of Pain

- Definition: the exertion of a modifying or controlling influence on something
- Occurs at nociceptor, in the spinal cord, and in the supraspinal structures
- Can either inhibit (suppress) or facilitate (intensify)



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Peripheral Modulation of Pain

- Facilitation
  - Nociceptors and their neurons display sensitization following repeated stimulation
    - Enhanced response to noxious stimulus
    - Or newly acquired response to other stimuli
      - Including nonnoxious
  - Primary hyperalgesia
    - Following injury and mediated by noxious substances released from tissue
- Inhibition
  - Peripheral exogenous opioid release

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Central Modulation of Pain

- Facilitation
  - Caused by three mechanisms
    - Wind-up and sensitization of second-order neurons
      - Increased frequency of discharge with repetitive stimulus even after it stops
    - Receptive field expansion
      - Dorsal horn increase receptive fields, adjacent neurons respond to stimuli when previously unresponsive
    - Hyperexcitability of flexion reflexes

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Central Modulation of Pain

- Inhibition
  - Segmental inhibition
    - Pain stopped in the second order neuron and spinothalamic tract
  - Supraspinal inhibition
    - Supraspinal structures send fibers down the spinal cord to inhibit pain at the dorsal horn

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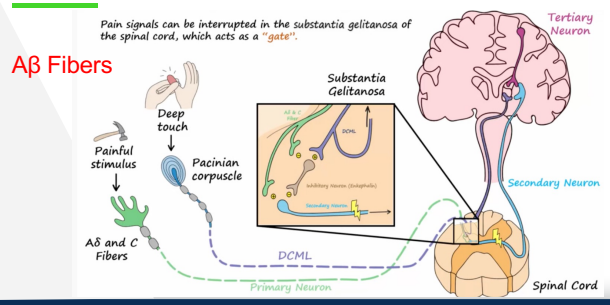
Gate Control Theory



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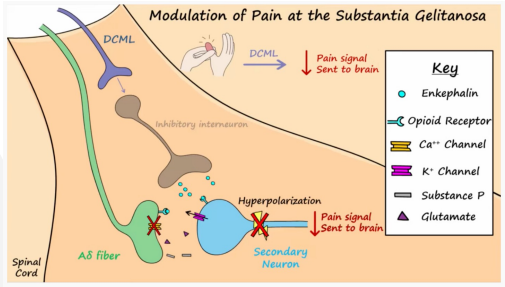
Gate Control Theory



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Perception

Perception	Describes processing of afferent pain signals in the cerebral cortex and limbic system • How we "feel" about pain

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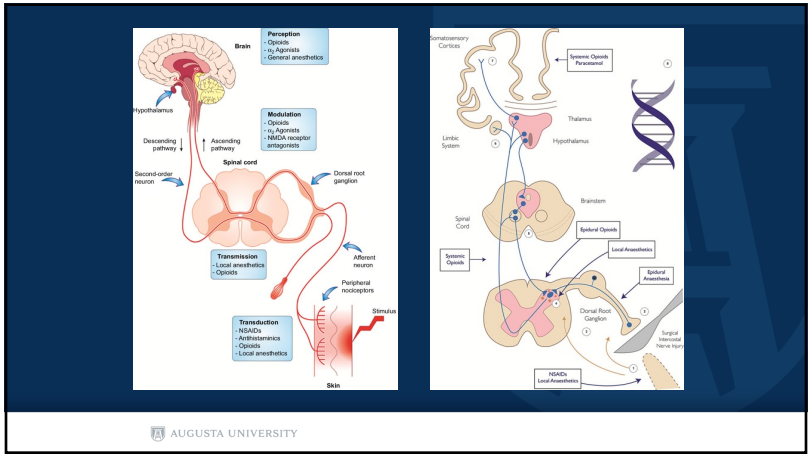
Brain
Perception
- Opioids
- α_2 Agonists
- General anesthetics
Hypothalamus
Modulation
- Opioids
- α_2 Agonists
- NMDA receptor antagonists
Descending pathway
Ascending pathway
Spinal cord
Second-order neuron
Dorsal root ganglion
Transmission
- Local anesthetics
- Opioids
Afferent neuron
Peripheral nociceptors
Stimulus
Transduction
- NSAIDs
- Antihistaminics
- Opioids
- Local anesthetics
Skin
Somatosensory Cortices
Systemic Opioids Paracetamol
Thalamus
Limbic System
Hypothalamus
Brainstem
Spinal Cord
Epidural Opioids
Local Anesthetics
Systemic Opioids
Epidural Anesthesia
Dorsal Root Ganglion
Surgical Intercostal Nerve Injury
NSAIDs
Local Anesthetics
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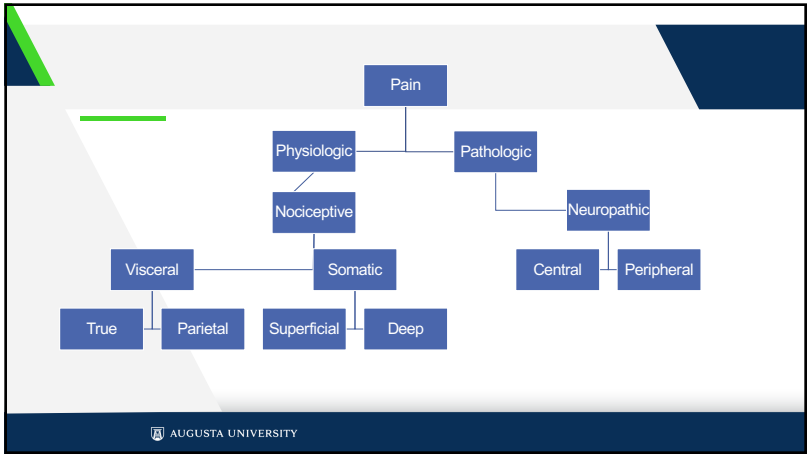
Pain
Physiologic
Pathologic
Nociceptive
Neuropathic
Visceral
Somatic
Central
Peripheral
True
Parietal
Superficial
Deep
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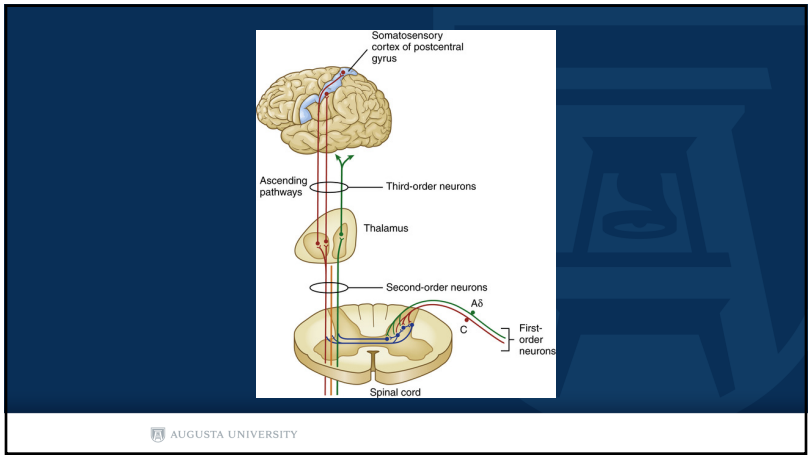
Somatosensory cortex of postcentral gyrus
Ascending pathways
Third-order neurons
Thalamus
Second-order neurons
Aδ
C
First-order neurons
Spinal cord
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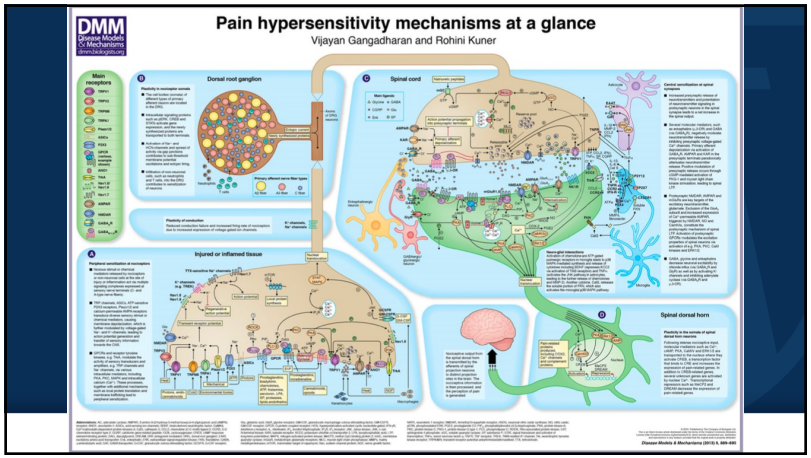
DMM
Disease Models & Mechanisms
dmm.biologists.org
Pain hypersensitivity mechanisms at a glance
Vijayan Gangadharan and Rohini Kuner
Main receptors
Dorsal root ganglion
Spinal cord
Injured or inflamed tissue
Spinal dorsal horn

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Acute Pain

- Short-lasting and manifesting in objective ways that can be easily described and observed
- **Nociceptive** is the most common cause
- Serves to detect, localize, and limit tissue damage
- Seen in post op, post trauma, fracture, etc

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Nociceptive Pain

- Derived from noci
  Latin for harm or injury
- Types of acute nociceptive pain
  - Somatic pain
  - Visceral pain

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Somatic Pain

- Can be further classified
  - Superficial
    - Due to nociceptive input from the skin, SQ or mucous membranes
    - Well localized
    - Sharp, pricking, throbbing, or burning
  - Deep
    - From muscles, tendons, joints, or bones
    - Dull, aching
    - Less well localized

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Visceral Pain

- Due to a disease process or abnormal organ function from an internal organ
  - From organ itself or its covering
    - Parietal plura, pericardium, etc
- Four subtypes
  - True visceral pain (localized or referred)
    - Dull, diffuse, and usually midline
    - Associated with symp or parasymp activity causing N/V, sweating, changes in BP/HR
  - Parietal pain (localized or referred)
    - Sharp, stabbing that is localized to the organ or distant site

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Chronic Pain

- No common understanding of characteristics, symptoms, or length
- Miller estimates between 20% to 60% of the population
- US annual cost $600 billion
  - Health care
  - Disability
  - Lost work days
  - Related Expenses

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Chronic Pain

- Extending in duration beyond the expected temporal boundary or tissue injury and normal healing
- More subjective
  - May develop from nociceptive pain but psychological and behavioral factors play a major role
- Not easily clinically characterized
- Affects a persons life and ability to function

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Chronic Pain

- Typically categorized as
  - Malignant
    - Related to cancer and its treatment
  - Nonmalignant
    - Neuropathic, musculoskeletal, inflammatory

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Not Just Sensory Pain

- Chronic Pain have influences in
  - Biological
    - Tissue damage
  - Cognitive
    - Memory, expectations
  - Emotional
    - Anxiety, depression
  - Environmental
    - Reinforcement, conditioning

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Chronic Pain Syndromes

- Somatic
  - Low back pain, degenerative disc, failed back surgery, bony metastases, Myofacial pain syndrome
- Visceral
  - Abdominal cancer, chronic pancreatitis
- Neuropathic
  - CRPS, post herpetic neuralgia, trigeminal neuralgia, phantom limb pain, spinal stenosis

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Neuropathic Pain

- Caused by injury to the nervous system
  - Result of tumor compressing nerve or spinal cord
  - Cancer actually infiltrating into nerves or spinal cord
  - Diabetic neuropathy

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What Can Lead to Chronic Pain?

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Chronic Pain

- How does it develop?
- Peripheral sensitization
  - Injury causes chemical release sensitizing area
  - Reduction in threshold and increase response to nociception
- Central sensitization
  - Membrane excitability, synaptic recruitment and decrease inhibition
  - Uncoupling of pain from peripheral stimuli

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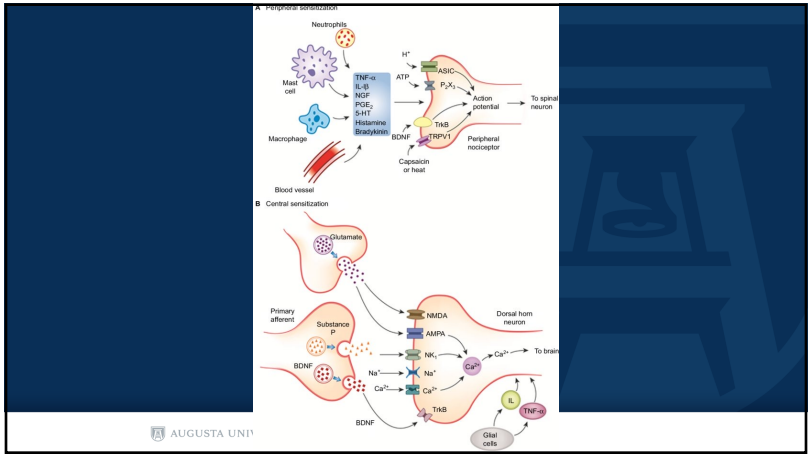

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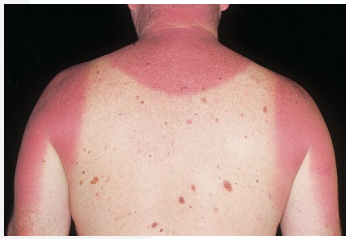
Sensitization



- Repeated stimuli reduces threshold of primary afferent nociceptors progressively
  - Repeated noxious stimuli may be continuous lasting for hours
  - Hot water > unbearable
  - Friendly slap on the back > excruciating

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Complex Regional Pain Syndrome

- Neuropathic pain disorder
- Largely undiagnosed
- Risk factors for developing CRPS
  - Previous trauma or surgery
  - Nerve injury (for Type II)
  - Work related injury
  - Female
- Two types
  - Type I (Reflex sympathetic dystrophy)
  - Type II (Causalgia)
  - Clinical features are the same except Type II had documented prior nerve injury

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Complex Regional Pain Syndrome

- S&S
  - Spontaneous pain
  - Hyperalgesia
  - Allodynia
  - Active and passive movement disorders

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Type 1 CRPS

- "Reflex Sympathetic Dystrophy"
- Pain disproportionate to injury
- Pain persists beyond the time the tissue-damaging process has ended
- Sympathetic nervous system clearly plays a major role
  - Sympathetic outflow can induce discharge of primary afferent nociceptors
  - Selective blockade of the sympathetic outflow provides relief

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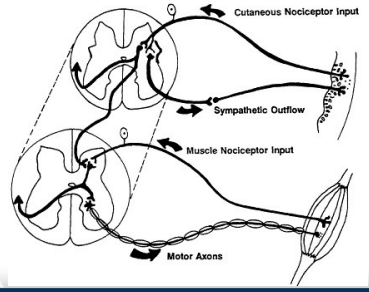
Reflex Sympathetic Dystrophy



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Muscle Contraction

- Nociceptor activity causes contraction in muscles
  - Sometime sustained
- Muscle Contraction can play a large role in chronic pain

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Chronic Postsurgical Pain

- CPSP
  - Occurs in 10% of surgical pts
  - Begins as "difficult to control" acute postoperative pain
  - Becomes persistent pain with neuropathic features unresponsive to opioids

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Chronic Postsurgical Pain

- Occurs at the site of surgery
- Persists a month longer than expected
- 3-6 months post-op
- Descriptors correlate with possibility of nerve damage during the surgical procedure
  - Hyperalgesia
  - Dysaesthesia
  - Allodynia

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Pain Therapy

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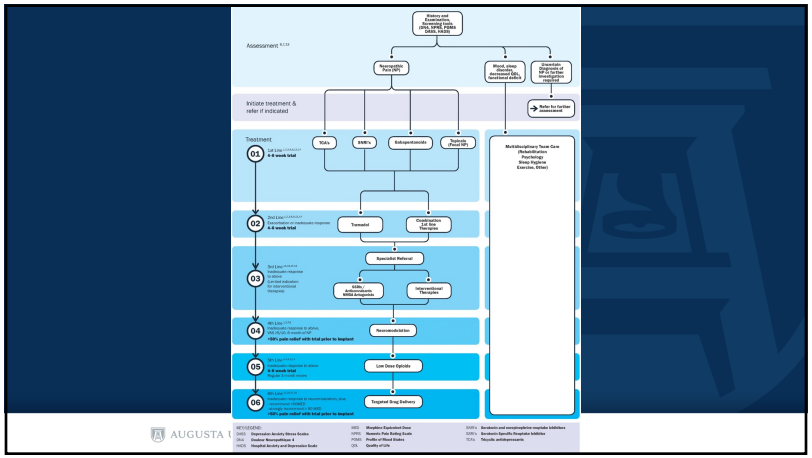

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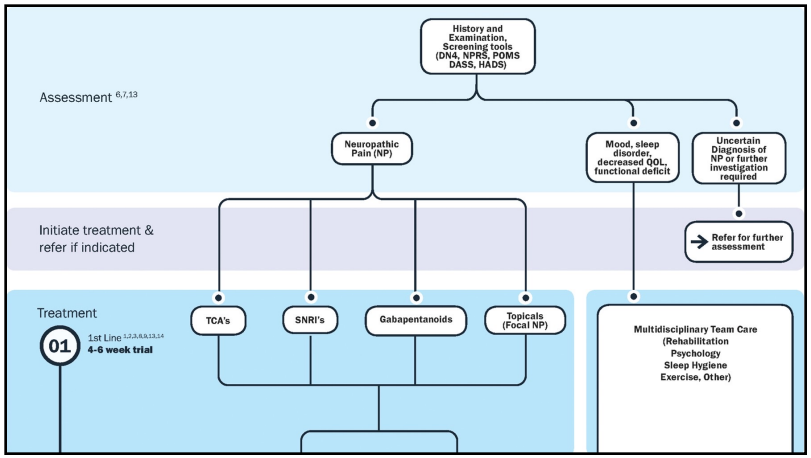

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Interdisciplinary Management of Chronic Pain

- Helpful in Chronic nonmalignamt pain
- Specialties
  - Psychology
  - PT
  - OT
  - Anesthesia

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Tricyclic Antidepressants

- Most studied antidepressants for the treatment of neuropathic pain
- Firstline therapy across multiple guidelines
  - Inhibition of serotonin and norepi re-uptake
  - Also block histamine, adrenalin, acetylcholine, and sodium channels
- Pain-relieving effect independent of antidepressant effect at 20–30% of the effective antidepressant dose

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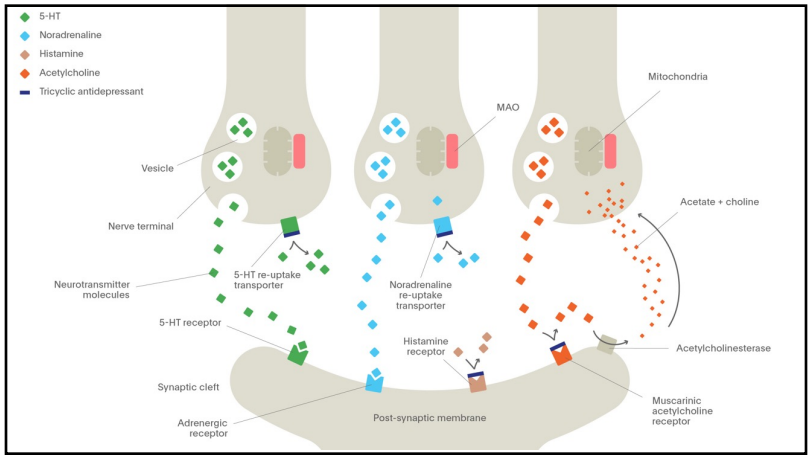

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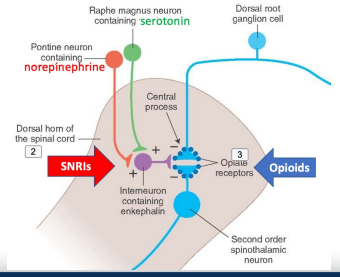
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- Firstline treatment in multiple international guidelines
  - Most commonly studied are duloxetine (Cymbalta) and venlafaxine (Effexor)
- MOA
  - Facilitate descending inhibition by blocking serotonin and noradrenaline reuptake
  - Effective in peripheral diabetic neuropathy, painful peripheral neuropathy
  - Effective in osteoarthritis, chronic low back pain, fibromyalgia, and depression



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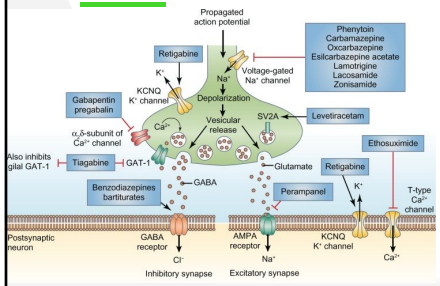
Anticonvulsants



- Gabapentin
  - Gralise, Neurontin, Horizant
  - 600 mg PO TID
  - Max daily dose = 3600 mg
- Pregabalin
  - Lyrica
  - 150 mg PO BID or TID
  - Max daily dose = 600 mg
- Carbamazepine

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Anesthesia & Analgesia (2012)

The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin

A Combined Systematic Review and Meta-Analysis

Clarke, Hance MSc, MD, FRCPC*,†,‡; Bonin, Robert P. PhD§; Orser, Beverley A. MD, PhD, FRCPC†,‡; Englesakis, Marina BA MLIS‖; Wijeysundera, Duminda N. MD, PhD, FRCPC*,‡,¶,#; Katz, Joel PhD**

- 11 trials, 8 studied gabapentin, 3 used pregabalin
- 4/8 gabapentin found periop admin decreased chronic pain more than 2 months after surgery.
- 2/3 pregabalin significant reduction in CPSP and improvement in postsurgical patient function
- Supports periop admin of gabapentin and pregabalin in reducing the incidence of CPSP

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Topical

- Lidocaine patches
  - works by decreasing ectopic firing of peripheral nerves
  - First or second-line for post-herpetic neuralgia
  - Ineffective in postsurgical neuropathic pain and diabetic peripheral neuropathy with allodynia or hyperalgesia

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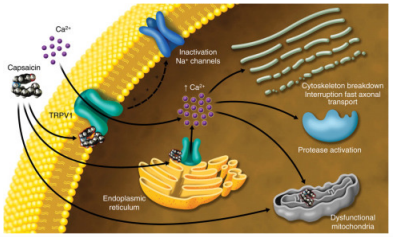
Topical

- Capsaicin
  - Binds to the TRPV1 receptor located on the Aδ and C-nerve fibers
  - Releases substance P and depolarizes nerve
  - Long-term exposure causes overstimulation, depletion of substance P, desensitization of the nerve, and reversible nerve degeneration
  - High-concentration capsaicin (8%) is recommended as third-line



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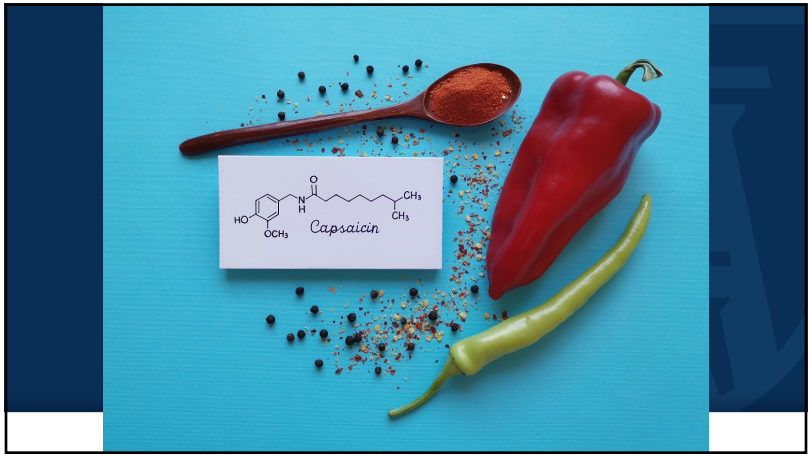

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Transdermal Substances

- Other possible topical drugs
  - May provide an alternative approach for some patients
  - Ketamine 10% shown to be effective in CRPS
  - Diclofenac may decrease burning in PHN and CRPS
  - Clonidine has limited effect in diabetic peripheral neuropathy
  - Amitriptyline 1–5% has been shown to be ineffective

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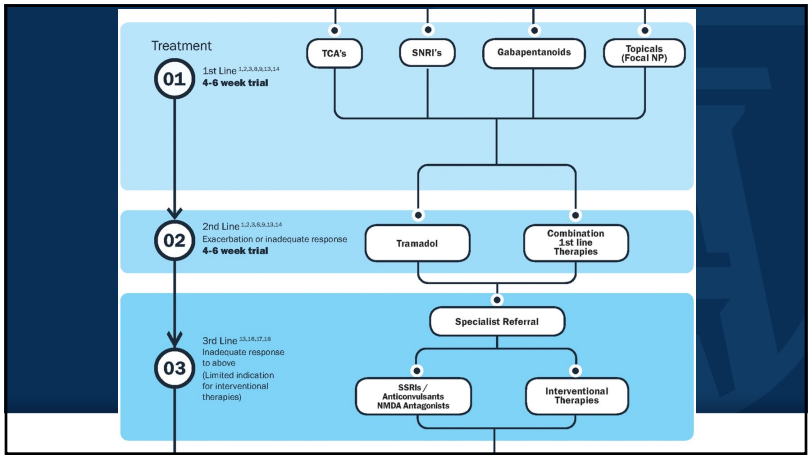

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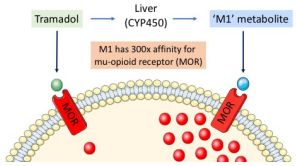
Tramadol

- Considered second-line treatment in most guidelines
- MOA
  - Weak μ-opioid agonist and inhibitor of serotonin and norepinephrine reuptake
- Effective in the treatment of neuropathy (diabetic, postherpetic and cancer-related)



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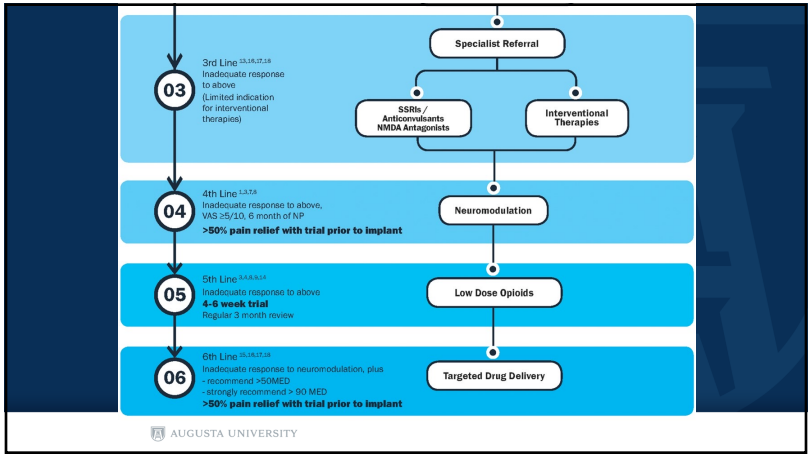

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Procedural Therapy

- Somatic blocks
  - Trigeminal nerve blocks, paravertebral blocks (cervical, thoracic, lumbar), facet blocks, trans sacral nerve blocks
- Sympathetic blocks
  - Stellate ganglion blocks, celiac plexus block, sympathetic chain block (thoracic, lumbar)
- Epidural
  - ESI, RFA
- Implantable stimulators
  - Spinal or Deep brain

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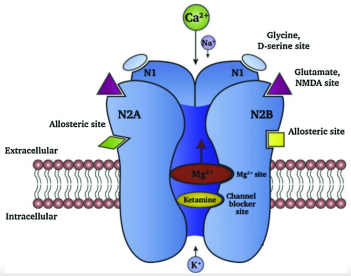
NMDA Antagonist

- Ketamine
  - New research focused on inhibition of Astrocyte activation
  - May stop the development and advancement of neuropathic pain at its source



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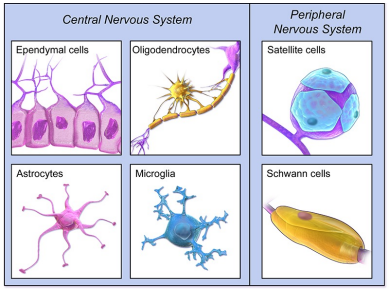
Neuroglia



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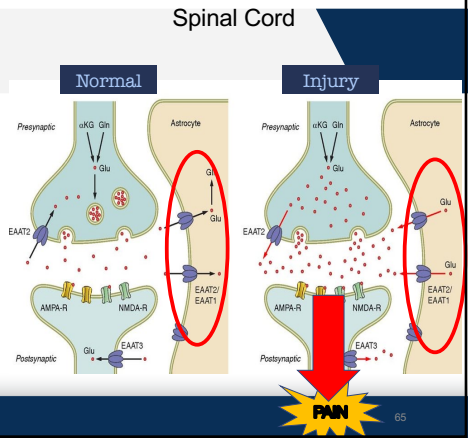
Glutamate & Glia

- Hallmark of neuropathic pain is elevated extracellular levels of glutamate
  - Increased presynaptic release
  - Impaired glutamate reuptake from glial cells
  - Results in increased pain sensation and transmission



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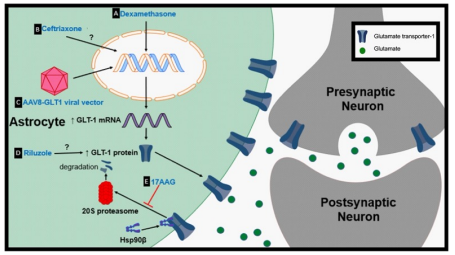
Upregulators of EAATs

- β-lactam: Ceftriaxone
- β-lactamase Inhibitor: Clavulonic Acid
- Anticonvulsants: Valproate & Riluzole
- Tricyclic antidepressants: Amitryptyline
- Gene Therapy



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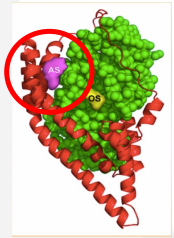
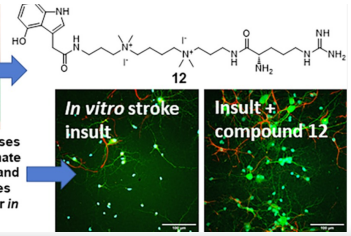
Positive Allosteric Modulators of EAATS

EAAT2 PAMs from parawixia bistriata spider venom



Compound 12 increases activity of glial glutamate transporters EAAT1 and EAAT2, and provides neuroprotection after *in vitro* stroke



Identified and isolated using MS and HPLC

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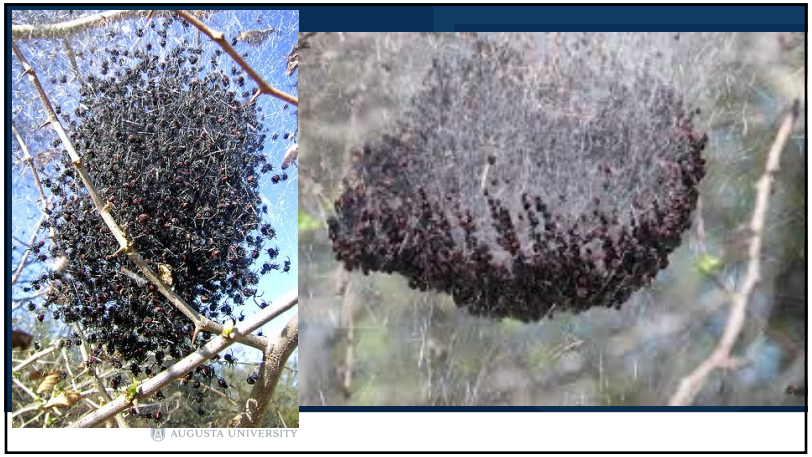

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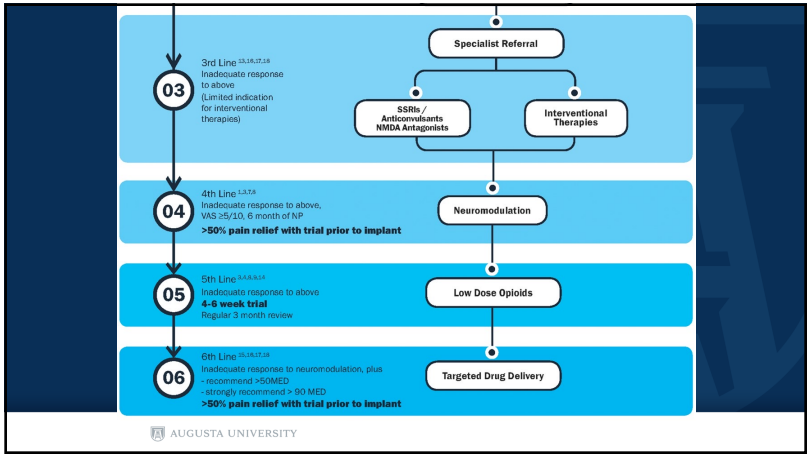

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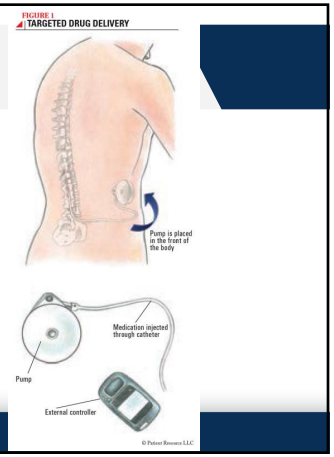
Targeted Drug Delivery

- Deliver medications to site of action at the dorsal horn
  - Bypasses first pass metabolism and the blood–brain barrier.
  - Increases the potency of the medication
  - Morphine and ziconotide
    - N-type calcium channel antagonist



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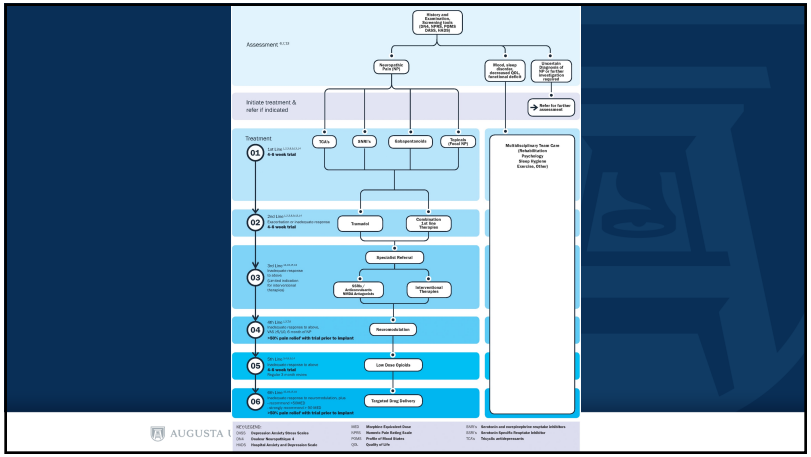

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References

- Apex Anesthesia Review.
- Barash, P. G. (2013). *Clinical anesthesia* (7th ed.). Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.
- Bates, D., Schultheis, B. C., Hanes, M. C., Jolly, S. M., Chakravarthy, K. V., Deer, T. R., ... & Hunter, C. W. (2019). A comprehensive algorithm for management of neuropathic pain. *Pain Medicine*, *20*(Supplement_1), S2-S12.
- Clarke, H., Bonin, R. P., Orser, B. A., Englesakis, M., Wijeysundera, D. N., & Katz, J. (2012). The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesthesia & Analgesia*, *115*(2), 428-442.
- Culp, C., Kim, H. K., & Abdi, S. (2021). Ketamine use for cancer and chronic pain management. *Frontiers in Pharmacology*, *11*, 2360.
- Falcucci, R. M., Wertz, R., Green, J. L., Meucci, O., Salvino, J., & Fontana, A. C. K. (2019). Novel positive allosteric modulators of glutamate transport have neuroprotective properties in an in vitro excitotoxic model. *ACS chemical neuroscience*, *10*(8), 3437-3453.
- Glare, P., Aubrey, K. R., & Myles, P. S. (2019). Transition from acute to chronic pain after surgery. *The Lancet*, *393*(10180), 1537-1546.
- InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. What is an inflammation? 2010 Nov 23 [Updated 2018 Feb 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279298/

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References

- Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior; Osterweis M, Kleinman A, Mechanic D, editors. Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives. Washington (DC): National Academies Press (US); 1987. 7, The Anatomy and Physiology of Pain. Available from: https://www.ncbi.nlm.nih.gov/books/NBK219252/
- Kuner, R., & Kuner, T. (2021). Cellular circuits in the brain and their modulation in acute and chronic pain. *Physiological Reviews*, *101*(1), 213-258.
- Miller, Ronald D. Miller's Anesthesia. 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier, 2010.
- Morgan, G. E., Mikhail, M. S., & Murray, M. J. 1. (2006). Clinical anesthesiology (4th ed.). New York: Lange Medical Books/McGraw Hill Medical Pub.
- Orhurhu, V., Orhurhu, M. S., Bhatia, A., & Cohen, S. P. (2019). Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials. *Anesthesia & Analgesia*, *129*(1), 241-254.
- Rajput, K., & Vadivelu, N. (2021). Acute Pain Management of Chronic Pain Patients in Ambulatory Surgery Centers. *Current Pain and Headache Reports*, *25*(1), 1-12.
- Saarto, T., & Wiffen, P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews*, (4).
- Underhill, S. (2014). Excitatory Amino Acid Transporters in Neurons and Glia.
- Wolozin, B. L., & Pasternak, G. W. (1981). Classification of multiple morphine and enkephalin binding sites in the central nervous system. *Proceedings of the National Academy of Sciences*, *78*(10), 6181-6185. https://doi.org/10.1073/pnas.78.10.6181

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