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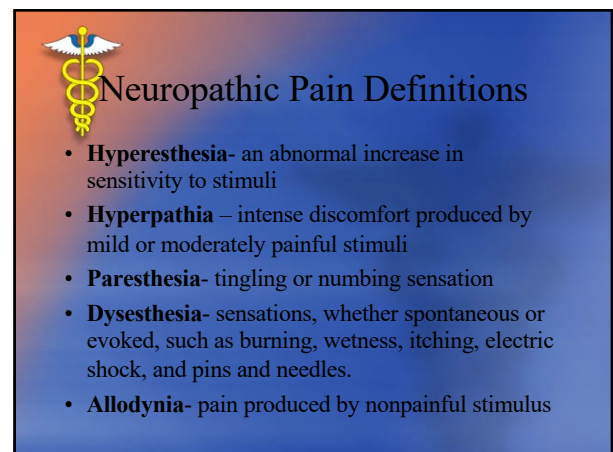
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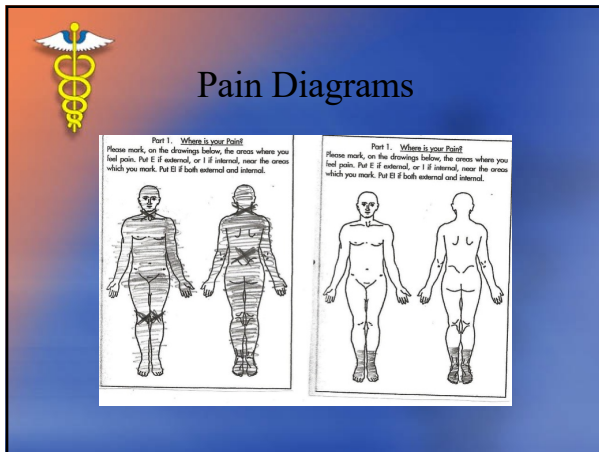
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Pathology-Neuropathic Pain

- Carpal Tunnel Syndrome / nerve compression
- Migraine
- Radicular pain- cervical/lumbar/amyotrophy
- Post herpetic neuralgia
- Peripheral neuropathy- DM, ETOH, idiopathic
- Complex Region Pain Syndromes
- Central pain (SCI/ Brain lesions
thalamic/multiple sclerosis/fibromyalgia
- Phantom limb pain

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Pain in the 17th century

The Cartesian model of pain (Descartes 1664) is responsible for many misconceptions about pain.

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Pain in the 21st century

- 1) C-fibers enter the Dorsal Horn of the spinal cord and form synaptic contacts with two discrete populations of "second order" spinal afferents.
- 2) The C-fibers release **glutamate**, which bind two types of post-synaptic receptors -AMPA for a fast excitatory response. -**NMDA** that heighten the response of second order neurons to subsequent stimulation (hyperalgesia)
- 3) The C-fibers also release substance-P that binds to neurokinin-1 (NK-1). Persistent activation of NK-1 remodels the synaptic organization of the dorsal horn.
- 4) C-fibers can retrogradely release substance-P and calcitonin to the tissues they innervate. These potent vasodilators release inflammatory substances from the vasculature.

2) A branch of the STT projects to the raphe nuclei and loci ceruleus. These nuclei respond by altering the synthesis of serotonin and norepinephrine which mediate mood, emotion, and cognition.

3) STT can also amplify opiate, serotonergic and noradrenergic pain modulation via "descending pathways" in the spinal cord.

4) Cortical neurons seem to have trouble accurately discriminating C-fiber input. This may impair the cortical capacity to modulate the pain signal thus further leading to the widespread somatic distress of the **chronic pain syndrome**.

1) The majority of the NS and WDR second order neurons that receive C-fiber input cross-over and ascend the **spinothalamic tracts (STT)**.

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Neuroplasticity (Nociplastic pain)

- **Neuroplasticity**, is the ability of the brain to change throughout an individual's life, e.g., brain activity associated with a given function can be transferred to a different location, the proportion of grey matter can change, and synapses may strengthen or weaken over time.
- Neuroplasticity can be observed at multiple scales, from microscopic changes in individual neurons to larger-scale changes such as cortical remapping in response to injury.

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Neuroplasticity

The Insular Cortex

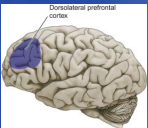
Insular Cortex (IC)- area of the brain involved in surveying how the body feels internally

- Chronic pain the IC becomes overactive causing it to process too many internal sensations associated with negative emotions
- Hypervigilance ensues leading to any internal sensation to be labeled as negative and painful

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Neuroplasticity

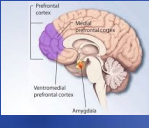


- **Dorsolateral Prefrontal Cortex**
- Area of cognitive thought and decision making
- Also area of the brain turns off the pain response.
- Pain catastrophizing, attention to pain, and the perceived inability to achieve goals.

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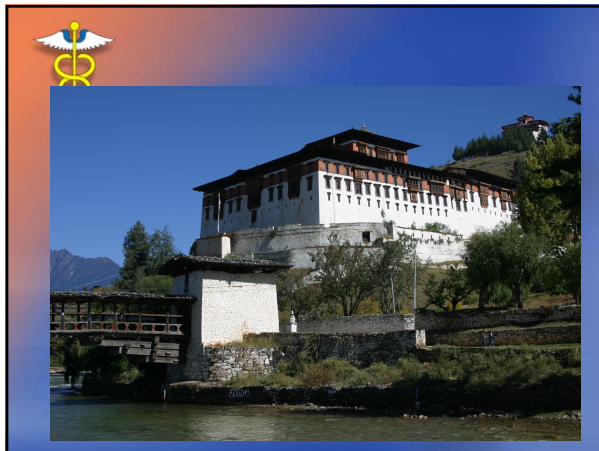
Neuroplasticity



- **Medial Prefrontal Cortex**
- Processes risk and fear –helps with making optimal decisions.
- Chronic pain leads (MPF) to make poor choices such as not exercising, avoiding healthy lifestyle changes – inability to get the body back on the correct course.



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Treatment of Neuropathic Pain

- Reduce inflammation
 - Reduce glial cell activation
 - Reduce inflammatory cytokines
- Peripheral Antinociception
 - Nerve secretion inhibition substance P, Neurokinini-1
- Reduction of Central Pain Pathway Hypersensitization
 - Reduce glutamate, Substance P, and NMDA receptor activation of the DRG, spinal cord lamina, Spinothalamic tracts, cerebral pain pathways
- ▶ Normalize sensory input

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Treatment of Neuropathic Pain

- First-Identify Underlying Cause and Treat Accordingly.
 - Blood glucose (DPN)
 - Structural pressure (CTS, Cubital tunnel)
 - Metabolic etiologies (TSH, B12, Vit D)
 - Functional deficiencies (muscle dysfunction)
 - Treat infectious etiologies /vaccinations (PHN)

Set Goals: reduce pain/improve function/reduce psychological distress/improve quality of life



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Treatment of Neuropathic Pain

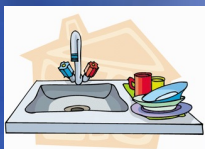
- **Exercise** is treatment for various diseases characterized by neuroinflammation. Exercise has been shown to decrease proliferation of microglia in the brain, decrease hippocampal expression of immune-related genes, and reduce expression of inflammatory cytokines such as TNF-alpha.
- **Rest ≠ Treatment**
- Change from Physician Centric treatment to Patient Centric self management

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Medical Management of Neuropathic Pain

- Multiple Targets exists in neuropathic pain:
 - Calcium & Sodium channels, opioid receptors, NMDA receptors, alpha-2 adrenoceptors, and serotonin/norepinephrine pathways.



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Neuroinflammation



- NSAIDs for Migraine, focal compression neuropathies
- Oral Steroid tapers radicular syndromes, MS, acute plexopathy, Migraine, CIDP, CNS vasculitis.
- Local steroid injections ACNES, focal compression neuropathies, coccydynia, Occipital neuralgias
- Epidural steroid injections for radicular syndromes, discopathies, zoster associated pain (not to prevent PHN)

*Cuckler. JBJS-1985; Bogduk, Spine Care-1995; Carrette. NEJM-1997; AHCPR-guidelines
*Cochrane Data Base Sys Rev. 2013 Mar.

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Topical Treatments

- Capsaicin cream .025-.075 tid-qid/ Patch 8%
 - Reduces Sub.P and blunts epidermal nociceptors
 - Poorly tolerated; erythema, pain, spread to eyes
- Lidocaine topicals 2.5% to 5% apply bid-tid
 - Inhibits Na⁺ channels however not deep penetrating.
- NeuroCreams; (great for meralgia paresthetica)
 - Creams better tolerated.

Compounding pharmacies






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Anticonvulsant Therapy

(influences Ca⁺⁺ influx of nerve endings reducing glutamate, substance P)

- Gabapentin 300 mg – 1200 mg up to tid
 - SE: dizziness, somnolence, peripheral edema
 - No plasma protein interactions
- Lyrica 50 mg – 300 mg bid
 - Better GI absorption
 - Titrates a bit quicker
 - Slightly lower SE profile (may need a PA)
- Topamax 25-50 mg q day to bid max 200 mg
 - Weight loss



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Antidepressants



- TCAs (nortriptyline, desipramine)
 - Inhibit norepinephrine & serotonin reuptake
 - anticholinergic SE blurred vision, sedation, constipation
 - Start low-10mg-and titrate at 2 week intervals
- SNRIs (duloxetine/venlafaxine)
 - Cymbalta 60 mg can help after one week

*SSRIs don't work well for pain but may help pain associated depression

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Opioids



- Short term benefit effective, however, Long-term efficacy for neuropathic pain is not well established with opioids.
- Methadone has some NMDA receptor blockade

Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105(1-2):71-78.

Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998;50(6):1842-1846.

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Complex Regional Pain Syndrome

sensory/vasomotor/sudomotor/trophic

- 1) Sympathetic blocks; stellate ganglion & lumbar chain.
- 2) Therapy / Therapy /Therapy
- 3) TENS units
- 4) Anticonvulsants and other pain Rx
- 5) Spinal Cord Stimulators
- 6) Multidisciplinary Pain Programs

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Postherpetic Neuralgia PHN



- Impact of chickenpox vaccination unknown incidence of developing PHN
- PHN increases with age 50% at 50, 60% at 60 etc.
- Vaccinations CDC recommends that healthy adults 50 years and older get two doses of the shingles vaccine separated by 2 to 6 months, to prevent shingles and PHN. (Shingrix instead of Zostavax)
- Antivirals during acute phase decreases viral shedding.
- Early sympathetic blockade for immediate pain relief and decreases incidence of PHN*

*J. Nelson. Acute Herpes Zoster Neuritis and Postherpetic Neuralgia. *Practice Pain Management* 2001 .

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Central Pain Treatment



- 1) **Patients Should Receive Education about Central Pain**
- 2) **Restorative Sleep** (good sleep hygiene/stress reduction/exercise/medications)
- 3) **Regular Exercise** (aerobic / resistance training)
Minimum 2-3 days per week 20 minutes
Goal 4-6 days per week 40 minutes
- 4) **Treat Underlying Psychiatric Disease**
– Depression / Anxiety / Bipolar
- 5) **Gain Control in the Patient's Life**
– Job / Spouse / Children /Victimization / Health issues
- 6) **Cognitive Behavioral Therapy**

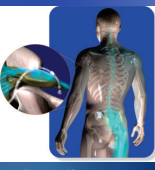
The Influence of age on fibromyalgia symptoms. Jaffe,M. *Journal of Aging Health* 2002

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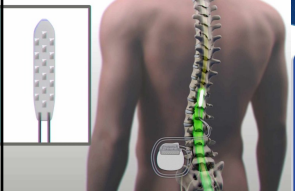


Neurostimulation

- Spinal Cord Stimulators
- Dorsal Root Ganglion stimulators



Dorsal Root Ganglion Stimulation



Dorsal Root Ganglion Stimulation (DRG)

New FDA Approved stimulation for chronic regional pain syndromes with a custom DRG targeted approach.

- Chronic, well-defined and Persistent Pain (e.g. Sciatic Pain)
- Lower Extremity and Visceral Pain
- CRPS I/II (Distal and Proximal)
- Peripheral Caudalgia, CRPS II (Proximal)
- Phantom and Stump Pain (Post Amputation)

Focal stimulation of the DRG offers patients a superior pain relief than traditional Spinal Cord Stimulation for Complex Regional Pain Syndrome (CRPS) and other focal chronic pain syndromes.

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Botulinum Toxins have Anecdotal Evidence in Neuropathic Pain

- BTs decrease neuritic pain post **Radiofrequency ThermoCoagulation** for facet arthropathy.
- BTs produce long-term benefit in **scar neuromas**.
- BTs produce long-term benefit in isolated **neuralgias**. (e.g. ilioinguinal)
- BTs produce long-term benefit in **phantom pain**.
- BTs produce long-term benefit in **migraine headaches**.*

*Blumenfeld, Botulinum Toxin Type A as an Effective Prophylactic Treatment in Primary Headache Disorder. *Headache* 2003;43:853-860



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What's New

- IV Ketamine – NMDA receptor blockade
- Glial Cell Deactivation for Central Pain
- Low Dose Naltrexone po 5 mg bid*
- Migraine Rx- atogepant (Qulipta) target calcitonin gene-related peptide (CGRP)
- Journavx 50 mg

*N= 31, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial 30% experienced a reduction in pain compared to 10% placebo -Arthritis Rheum. 2013

**Studies show that the monoclonal antibodies cut the number of headache days by 50% or more in around half of people who take them

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Thank You

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