Learning Objectives

▪ Understand and identify the types of pain fibers and classifications
▪ Understand and be able to explain current pain theories.
▪ Understand the neurophysiology in pain, as well as the pathophysiology in the development of chronic pain.

Learning Objective

▪ Understand pathological concepts in pain and learn how to diagnose and manage these conditions early in their development / presentation
Definition of Pain

- McCaffery (1968)
  - Pain is "whatever the experiencing person says it is, existing whenever he/she says it does".
- IASP (1979)
  - Pain is "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Pain Classification

- **Duration**
  - Acute
  - Chronic
- **Pathophysiology**
  - Nociceptive
  - Inflammatory
  - Neuropathic
Types of Afferent Nerve Fibers

<table>
<thead>
<tr>
<th>Type of Nerve Fiber</th>
<th>Information Carried</th>
<th>Myelin Sheath?</th>
<th>Diameter (micrometers)</th>
<th>Conduction Speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-beta</td>
<td>proprioception</td>
<td>hypereicin</td>
<td>13 - 20</td>
<td>80 - 120</td>
</tr>
<tr>
<td>A-alpha</td>
<td>touch</td>
<td>hypereicin</td>
<td>0.12</td>
<td>30 - 50</td>
</tr>
<tr>
<td>A-beta</td>
<td>pain (mechanical and thermal)</td>
<td>hypereicin</td>
<td>1 - 2</td>
<td>2 - 45</td>
</tr>
<tr>
<td>C</td>
<td>pain (mechanical, thermal, and visceral)</td>
<td>no hypereicin</td>
<td>0.2 - 1.0</td>
<td>0.6 - 3.0</td>
</tr>
</tbody>
</table>

Types of Afferent Nerve Fibers

Primary Afferent Axons

<table>
<thead>
<tr>
<th>Type</th>
<th>Size (μm)</th>
<th>Conduction Speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-alpha</td>
<td>15 - 50</td>
<td>80 - 120</td>
</tr>
<tr>
<td>A-beta</td>
<td>0.12</td>
<td>30 - 50</td>
</tr>
<tr>
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</tr>
<tr>
<td>C</td>
<td>0.2 - 1.0</td>
<td>0.6 - 3.0</td>
</tr>
</tbody>
</table>

Types of Pain Fibers
Example: Innervation of IVD

Nociceptors

- Sensitive to repeated or prolonged stimulation
- Mechanosensitive
- Excited by stress and tissue damage
- Chemosensitive
  - Excited by the release of chemical mediators
    - Bradykinin
    - Histamine
    - Prostaglandins
    - Arachidonic Acid
- Primary Hyperalgesia – Due to injury (Nociceptive)
- Secondary Hyperalgesia – Due to spreading of chemical mediators (Inflammatory)

Neuropathic Pain
Definition

- Neuropathic pain involves the combination of positive and negative symptoms in patients in whom pain is due to pathologic changes of neural tissue (Devor et al).
- Positive symptoms include pain, paresthesia, and spasm.
- In contrast, anesthesia and weakness are negative sensory and motor symptoms.
- Combination of positive and negative symptoms may broadly differentiate neuropathic pain from nonneuropathic; however, this may not always be the case, and so may be difficult to differentiate.
- Some disorders may consist of “mixed” pain, whereby neuropathic and inflammatory pain mechanisms coexist (Walsh et al).

Neuropathic Pain

- Simply stated, neuropathic pain is present when the neural tissue itself is or becomes the primary pain generator.

Neuropathic Pain: Common Perception

- Noxious and neuropathic pain may coexist in low back pain conditions.
Neuropathic Pain: Symptoms

- Perception of spontaneous pain without identifiable stimulus.
- Hyperalgiesia
  - Exaggerated responses to painful stimuli
- Allodynia
  - Pain with normally nonpainful stimuli

Pain Differentiation

Neuropathic Pain: Perpetuating Factors

The Inter-Relationship Between Pain, Sleep, and Anxiety / Depression
Neuropathic Pain: Etiology

Neuropathic Pain Etiology

Neuropathic Pain Comorbid Symptoms
Graphing Hyperalgesia and Allodynia

Pathophysiology of Neuropathic Pain

Neuropathic Pain: DDx
Neuropathic Pain: Diagnostic Tools

**Diagnostic Aids**
- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale (Bennett, Pain, 2001)
- DN4 Pain Questionnaire (Bouhassira et al. Pain, 2004)
- Neuropathic Pain Questionnaire (Ramundo and Kruse, Clin J Pain, 2010)
- Neuropathic Pain Scale (Laker et al. Neurology 1997)

**Pain Intensity / Characteristics**
- VAS
- Pain Likert Scale
- McGill Pain Questionnaire
- Neuropathic Pain Symptom Inventory (Bouhassira et al. Pain, 2004)

Neuropathic Pain: Screening Questionnaires

**J Clin Epidemiol. 2015**
- 37 studies were included.
- Evaluated measurement properties of:
  - DN4
  - LANSS
  - PainDETECT
  - Neuropathic Pain Questionnaire

**Conclusion**
- "DN4 and Neuropathic Pain Questionnaire were most suitable for clinical use."
- Should not replace a thorough clinical assessment.

Questionnaires for Neuropathic Pain Syndrome

**S-LANSS**
- Leeds Assessment of Neuropathic Symptoms
  - S-LANSS score of 12 indicates neuropathic pain.
  - Questionnaire takes a few minutes and identifies up to 80%
- * Screening tests will fail to identify up to 20% of patients with neuropathic pain.

**DN4**
- Douleur Neuropathique 4 Questions
  - DN4 score of 4 or more indicates neuropathic pain.
  - Takes slightly longer due to clinical exam component.
  - 83% sensitivity and 90% specificity.
- * Clinical assessment remains the standard for diagnosing neuropathic pain.
Neuropathic Pain: Conservative Treatment

Nonpharmacologic Options
- AMT
- Acupuncture
- TENS
- Biofeedback
- Relaxation Therapy
- Physical and Occupational Therapy
- Cognitive / Behavioral Strategies

Neuropathic Pain: Pharmacologic Agents

- Carbamazepine
- Trigeminal neuralgia
- Gabapentin
- Tegretol MRI
- Pregabalin
- Depakote
- Gabapentin
- Lidocaine Patch 5%
- Neurontin
- Neurontin MRI
- Neurontin TENS
- Tegretol MRI
- Tegretol
- Tegretol TENS
- Topical medications
- Systemic medications
- Interventional techniques

*Consider interventional pain control if previous treatments were unsuccessful.*
FDA-Approved Treatments for Neuropathic Pain

- Carbamazepine
- Topiramate
- Duloxetine
- Pregabalin for diabetic neuropathy
- Gabapentin
  - Postherpetic neuralgia
- Lidocaine esters
  - Postherpetic neuralgia
- Pregabalin
  - Peripheral diabetic neuropathy
  - Postherpetic neuralgia

Neuropathic Pain: Interventional Treatments

- Neural blockade
  - Sympathetic blocks for CRPS-I and II (reflex sympathetic dystrophy and causalgia)
- Neurolytic techniques
  - Alcohol or phenol neurolysis
  - Pulse radio frequency
- Stimulatory techniques
  - Spinal cord stimulation
  - Peripheral nerve stimulation
- Medication pumps

Example: RF for Facet Mediated Pain

Neuropathic Pain affecting the MBB resulting in chronic facet mediated pain.
Quantitative Sensory Testing (QST)

**EMG/NCV**
- Neurophysiological examinations to support a proximal nerve root lesion include the distal motor latency and the conduction velocity of motor fibers from the affected root.
- They also assess nerve conduction velocities and detect pathological values if motor fibers are involved in the damage. Sensory conduction studies are usually normal if the lesion is located distal to the dorsal root ganglion.
- Therefore, they do not help with the diagnosis. Somatosensory Evoked Potentials, which involve the entire afferent conduction from the periphery to the brain, are used to detect a central damage of sensory fibers (e.g., in the nerve root). However, it is important to understand that these conventional electrophysiological techniques only assess the function of myelinated peripheral axonal systems; the affection of small fibers, including nociceptors, are missed (Freynhagen et al. The Evaluation of Neuropathic Components in Low Back Pain. Current Pain & Headache Reports 2009, 13:188).

**QST**
- Quantitative Sensory Testing (QST), the standardized extension of the clinical neurophysiological sensory examination, allows the complete assessment of all sensory modalities by testing both large sensory fibers and the small fibers. It detects not only hypoperception but also hyperperception due to a disturbed pain processing in the periphery, spinal cord, or brain. QST is used to reveal pathological mechanisms involved in neuropathic pain and is recognized as a useful additional diagnostic tool (Freynhagen et al. The Evaluation of Neuropathic Components in Low Back Pain. Current Pain & Headache Reports 2009, 13:188).
Descartes: Straight Through Sensory Projection (1664)

- Proposed 3 centuries earlier
- Concept of pain was a specific, straight-through sensory projection system.
- This rigid anatomy of pain in the 1950s led to attempts to treat severe chronic pain by a variety of neurosurgical lesions.

Specificity Theory (Descartes)

- Development of Conceptual Models of Pain Mechanisms
Gate Control Theory (Melzack & Wall, 1965)

- Gating mechanism exists within the dorsal horn of the spinal cord.
- Small nerve fibers (pain receptors)
- Large nerve fibers (“normal” receptors)
- These two fibers synapse on Projection Cells (P), which go up the spinothalamic tract to the brain, and inhibitory interneurons (I) within the dorsal horn.
- The interplay among these connections determines when painful stimuli proceed to the brain.

Gate Theory

- When no input comes in, the inhibitory neuron prevents the Projection Neuron from sending signals to the brain (gate is closed).
• Normal somatosensory input happens when there is more large-fiber stimulation (or only large-fiber stimulation).
• Both the Inhibitory Neuron and the Projection Neuron are stimulated, but the Inhibitory Neuron prevents the Projection Neuron from sending signals to the brain.
• Gate is closed.

• Nociception (pain reception) happens when there is more small-fiber stimulation or only small-fiber stimulation.
• This inactivates the Inhibitory Neuron, and the Projection Neuron sends signals to the brain informing it of pain.
• Gate is open.

Gate Theory

Example

Bumping Elbow

Initial trauma activates the A-delta and, eventually, C fibers. Rubbing the traumatized area stimulates the A-beta fibers, which activate the Inhibitory Neuron (I) to close the spinal gate. Results in inhibition of the transmission of painful stimuli.
Factors Which Can "Open the Gate"

- Physical Conditions
  - Extent of injury
  - Nature of injury

- Emotional States
  - Anxiety
  - Worry
  - Tension
  - Depression

- Cognitive States
  - Focusing on the pain
  - Boredom

- Lack of Activity
  - Minimal / No Fitness
  - Minimal / No Exercise

Group Activity: Devise & Justify Treatment Plan

**History / Subjective**
- Female 30 yoa with LBP from WC injury (one year earlier) while bending over to clean under a sink.
- Sharp, stabbing LBP belt line distribution
- Lt anterolateral thigh burning
- Pain equal with sitting/standing
- Ibuprofen no help
- Pain Scale: 7/10 (6/10 & 8/10)

**Objective / Diagnostics**
- 5’3”, 160 lbs.
- Diffuse lumbar tenderness; all orthopedic testing positive (husband helped her change positions on exam table)
- Waddell’s +5/5
- MRI: Mild bulges L3-4 & L5-S1 with mild IVF narrowing.
- EMG/NCV studies negative
- FCE Valid for Light Work

Gate Theory: Unanswered Questions

- Gate Theory
  - Has been widely accepted, but it leaves unanswered questions, such as:
    - Chronic Pain Issues
    - Sex-Based Differences
    - Effects of Previous Pain Experiences
    - Phantom Pain
Phantom Limbs / Paraplegics

- Observations that don’t fit the theory.
- Peripheral and spinal processes are an important part of pain.
- However, data on painful phantoms below the level of total spinal section (Melzack 1989, 1990) indicate that we need to go above the spinal cord and into the brain.

Neuromatrix Theory

- In 2001, Ronald Melzack came up with a newer theory of pain that answered some of these questions. This new theory, the Neuromatrix Theory, stipulates that every human being has an innate network of neurons that they named the “Body-Self Neuromatrix”.

- Each person’s matrix of neurons is unique and is affected by all facets of the person’s physical, psychological, and cognitive traits, and also by their experience.
Neuromatrix Theory

Essentially, the model of the Neuromatrix Theory states that the central nervous system (CNS), which is made up of the brain and spinal cord, is where pain is produced and that multiple parts of the brain and spinal cord work together in response to stimuli from the body and/or environment to create the experience of pain.

This theory involves two important shifts in our understanding of pain:

1. The brain and spinal cord are what produce pain, not tissue damage.

2. Various parts of the CNS work together to produce pain.

Descartes for the Modern Age

Descending Pain Modulatory System
Central Sensitization

CHRONIC "PSYCHOSOMATIC" PAIN MAY HAVE ORGANIC BASIS

Definition

- Central Sensitization
  - Condition of the nervous system that is associated with the development and maintenance of chronic pain. When central sensitization occurs, the nervous system goes through a process called "wind-up" and gets regulated in a persistent state of high reactivity.

NIH: J Pain 2009

- Latremolier and Woolf
  - "Because CS results from changes in the properties of neurons in the CNS, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli."
  - "Instead, CS produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations."
CS contributes to the following clinical syndromes:
1. Rheumatoid arthritis
2. Osteoarthritis
3. Temporomandibular disorders
4. Fibromyalgia
5. Misc. Musculoskeletal Disorders
6. Headache
7. Neuropathic Pain
8. Complex Regional Pain Syndrome
9. Post-surgical Pain
10. Visceral Pain Hypersensitivity
Has CS Been Received Well?

<table>
<thead>
<tr>
<th>Accused and Labeled:</th>
<th>Woolf (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Secondary Gain</td>
<td>“We can now 30 years later, based on data from many studies in human volunteers, address whether central sensitization, defined operationally as an amplification of neural signaling within the CNS that elicits pain hypersensitivity, is a real phenomenon or not and can assess its relative contribution to inflammatory, neuropathic and dysfunctional pain disorders in patients.”</td>
</tr>
<tr>
<td>• Opioid Drug Seeker</td>
<td></td>
</tr>
<tr>
<td>• Malingering</td>
<td></td>
</tr>
<tr>
<td>• Liar</td>
<td></td>
</tr>
<tr>
<td>• Hysteric</td>
<td></td>
</tr>
<tr>
<td>• Psychosomatic</td>
<td></td>
</tr>
<tr>
<td>• Somatoform Disorder</td>
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</tbody>
</table>

Central Sensitization: Two Main Components

<table>
<thead>
<tr>
<th>Allodynia</th>
<th>Hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Experience of pain with things that are normally not painful.</td>
<td>• Occurs when an actual painful stimulus is perceived as more painful than it should.</td>
</tr>
<tr>
<td>• Light touch</td>
<td></td>
</tr>
<tr>
<td>• Massage</td>
<td></td>
</tr>
<tr>
<td>• Jump Sign</td>
<td></td>
</tr>
</tbody>
</table>

Pain Sensation / Response

![Graph showing the relationship between stimulus intensity and pain sensation/reaction with Allodynia, Hyperalgesia, and Normal states.](image-url)
### Central Sensitization: Less Common Characteristics

- Can lead to heightened sensitivities across all senses, not just the sense of touch:
  - Photophobia
  - Phonophobia
  - Odor
  - Cognitive Deficits
    - Poor Concentration
    - Poor Short-Term Memory
  - Increased Level of Emotional Distress
  - Anxiety
  - Sick Role Behaviors
    - Rest / Malaise
    - Pain Behavior

### Central Sensitization: Associated Chronic Conditions

#### Peripheral
- Low Back Pain
- Chronic Neck Pain
- Whiplash Injuries
- Chronic Tension HA
- Migraine HA
- Rheumatoid Arthritis
- OA of Knees
- Endometriosis
- Post-Surgical

#### Central
- Fibromyalgia
- Irritable Bowel Syndrome
- Chronic Fatigue Syndrome
- Common denominator of Central Sensitization

### Central Sensitization Syndrome

Root Cause of Multiple Chronic Pain Conditions
Central Sensitization: Causes in Peripheral Lesions

- Multiple Factors
  1. Factors that are associated with the state of the CNS prior to the onset of original injury or pain condition (Predisposition)
  2. Factors that are associated with the CNS following onset of original injury or pain condition (Antecedent Factors)

Central Sensitization: Predisposing Factors

- Psychophysiologic Factors
  - Stress
  - Anxiety
  - Psychological Trauma
  - Physical Trauma
  - Depression
  - Genetic

Central Sensitization: Antecedent Factors

- Subsequent development of:
  - Depression
  - Fear Avoidance
  - Anxiety
  - Poor Sleep
  - Operant Learning
    - Interpersonal Reinforcements
    - Environmental Reinforcements
    - Iatrogenic Reinforcement
Excitation vs. Inhibition

Central Sensitization: Two Distinctly Different Approaches

1. Address effects of CS after it has occurred.
2. Interrupt the CS and let the body’s homeostatic mechanisms clear residual pathologic products.
   ▪ Within these two categories there are pharmacological and non-pharmacological therapeutic options.

Central Sensitization: Treatment Complications

1. “Polypharmacy is one of the problems attendant to CSS therapy, and is the result of approaching each of the varied presentations of CSS as a separate and distinct disease.”
2. “...failure to differentiate acute pain from chronic pain.”
3. “...essential to treat the pathways in chronic pain disease.”
Central Sensitization: Non-Pharmacological Approaches

- Manual Therapy
- Percutaneous Electoneural Stimulation (PENS)
- Improving Stress Tolerance and Neuro feedback Training
- TENS
- Virtual Reality

Central Sensitization: Pharmacological Approaches

Address Effects of CS
- Acetaminophen
- Serotonin (SSRI) and Norepinephrine (SNRI) reuptake inhibitors
- Tricyclic antidepressants (TCA)
- Opioids and Tramadol

Treat CS Itself
- N-methyl-D-aspartate (NMDA) receptor blockers
- Calcium channel alpha(2) ligands
- Gabapentin
- Pregabalin

Central Sensitization: Treatment

- Interdisciplinary Chronic Pain Rehabilitation Program (CPRP)
- Health Psychology
- PT / Chiropractic
  - Must avoid too aggressive treatment (hypervigilant CNS)
    - Must show “Sensitivity to Sensitivity”
- Medication
  - Target CNS (antiepileptics and antidepressants)
  - NSAIDS and other medications which target the peripheral tissues are ineffective

Interdisciplinary Pain Management

- Physical Therapy
- Occupational Therapy
- Rehabilitation
- Social Work
- Psychology
- Nursing
- Other medical professionals

CNS: Central Nervous System

Note: Treatment options may vary based on individual circumstances and should be discussed with a healthcare provider.
Opioid-Induced Hyperalgesia (OIH)

Be wary of OIH...

- State of nociceptive sensitization caused by exposure to opioids.
- Suspect OIH:
  1. Opioid treatment effects wane in the absence of disease progression.
  2. Unexplained pain reports or diffuse allodynia unassociated with the original pain.
  3. Increased level of pain with increased opioid dosages.

Placebo Effect

- Placebo is derived from the Latin work for “I shall please”.
- Used to describe pain reduction obtained from a mechanism other than those related to the physiological effects of the treatment.
- All treatments have some degree of placebo effect.
- Most reputable studies utilize some type of “sham” treatment for comparison.
- Ultrasound set at the intensity of 0 and an actual treatment have shown decreased levels of pain in each group.
Common Knee Surgery No Better Than Placebo

- Patients with OA of knee who underwent placebo arthroscopic surgery were just as likely to report pain relief as those who received the real procedure, according to the Department of Veterans Affairs and Baylor College of Medicine.

Placebo Response and Neuromatrix Model

- Neuromatrix Model of pain puts what we know about the Placebo Response in a new light.
- Perhaps the Placebo Response is not so mysterious; nor should it be so “taboo”
- What if, all along, the Placebo Effect has been an unintentional cognitive behavioral intervention that changes the neuromatrix of the brain’s responses and thereby reduces pain?

Nocebo Effect

- Placebo has an Evil Twin Named “Nocebo”
  - Just as expectations of a treatment’s effectiveness can influence the reaction to a placebo, an expectation of side effects can cause a patient to experience them as well.
- Study on Finasteride for Enlarged Prostate
  - Half were told by the doctor that erectile dysfunction was a possible side effect and the other half were not.
  - Of the group told about ED, 44% reported ED compared to only 15% of that group that was not told.

- Do you know of any “physicians” taking advantage of the Nocebo Effect?

Nocebo: A harmless thing that causes harm because you believe it’s harmful.
Central Sensitization: Thoughts

- Represents a “Neurologic Meltdown”
- Researchers now believe Central Sensitization is a major common denominator in most difficult pain problems.
- May be the universal factor that puts the “chronic” in chronic pain, giving all such problems characteristics regardless of how it got started – not the cause of the pain, but perhaps the cause of its chronicity.
Central Sensitization Inventory
Screening instrument for help in identifying CSS (Central Sensitivity Syndrome)


Revisit Chronic LBP Patient

- After History & Evaluation
- Administered Central Sensitization Inventory
  - Part A
    - Score equal or greater than 40 considered positive for Central Sensitization.
    - Patient scored 92
  - Part B
    - Significant for Central Sensitization Syndromes
CSI Part B

- Significant for:
  - Migraine Headaches
  - Irritable Bowel Syndrome
  - Depression
- All diagnosed in 2015
- What's the significance?

WC Patient

DIAGNOSTIC ENHANCEMENT

Psychiatric comorbidity (W31.011):

- Primary Diagnosis:
  - Migraine Headaches
- Secondary diagnoses:
  - Irritable Bowel Syndrome
  - Depression
- All diagnosed in 2015

Patient Explanation
Case Studies