NEUROPATHIC PAIN

What We Need to Know!
Under Accreditation Council for Continuing Medical Education guidelines, disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

**Alexander Bautista, MD**

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Nature of Relevant Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>What was received?</td>
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<tr>
<td>None</td>
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The conflict was resolved by
Relevant Disclosure and Resolution

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Alexander Bautista, MD

I have no relevant financial relationships or affiliations with commercial interests to disclose.
Experimental or Off-Label Drug/Therapy/Device Disclosure

I will NOT be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.
Objectives

■ Understand and identify different neuropathic pain conditions
■ Properly assess patients with neuropathic pain
■ Establish a rational treatment plan
Pain

IASP Definition

“Pain is an unpleasant SENSORY and EMOTIONAL experience associated with actual or potential tissue damage or described in terms of such damage.”
- 40% visits to primary care each year
  - 20% have more than 6 months
- Chronic pain: source of severe pain and suffering; work absenteeism
- Needs EARLY diagnosis and treatment

Mantyselka, et. al. Pain 2001; Maniadakis Pain 2000
THREE MAIN TYPES OF PATHOPHYSIOLOGY can be considered to result in chronic pain

**NOCICEPTIVE PAIN**
- Pain related to *damage of somatic or visceral tissue*, due to trauma or inflammation
- Examples: Rheumatoid arthritis, osteoarthritis, gout

**NEUROPATHIC PAIN**
- Pain related to *damage of peripheral or central nerves*
- Examples: Painful diabetic peripheral neuropathy, postherpetic neuralgia

**SENSORY HYPERSENSITIVITY**
- Pain without identifiable nerve or tissue damage, hypothesized to result from persistent neuronal dysregulation—may be called Fibromyalgia

More than 1 type of pain may be present in a given patient
The Continuum Of Pain

Time to resolution

Insult

Acute Pain

<1 month

• Usually obvious tissue damage
• Increased nervous system activity
• Pain resolves upon healing
• Serves a protective function

Chronic Pain

≥3-6 months

• Pain for 3–6 months or more
• Pain beyond expected period of healing
• Usually has no protective function
• Degrades health and function

If you think you're tired of listening to me talk about my chronic pain, just imagine how tired I am of having it.
NEUROPATHIC PAIN
What is Neuropathic Pain?

- IASP: “Pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system”
- Clinical practice
  - Etiology
  - Anatomical location of the lesion
What is Neuropathic Pain?

Neuropathic Pain
Pain caused by a lesion or disease of the Somatosensory nervous system

Peripheral Neuropathic Pain
Pain caused by a lesion or disease of the Peripheral somatosensory nervous system

Central Neuropathic Pain
Pain caused by a lesion or disease of the Central somatosensory nervous system
Neuropathy

- Sensory \( \rightarrow \) tell us how we feel
- Motor \( \rightarrow \) stimulate muscle contractions
- Autonomic \( \rightarrow \) control functions that our bodies don’t consciously regulate such as breathing and heart rate
Prevalence

- The prevalence of neuropathic pain is 6-8%
Prevalent Forms of Neuropathic Pain

Diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are the most common forms of neuropathic pain.
Neuropathic Pain is a Disease
PATHOPHYSIOLOGY

Injury → Free nerve ending Aδ and C fiber → Wallerian degeneration with immune cells → Bradykinin, serotonin, NA → Hyperalgesia, allodynia

Increased expression of Na channel → Central facilitation at spinal dorsal horn → Increased excitability of central neurons

Spontaneous nerve discharge → Cortical reorganization → CRPS, phantom limb pain

Paresthesias
Diagnosing Neuropathic Pain is Challenging
Neuropathic Pain vs Muscle Pain

- Burning
- Stabbing
- Electric shock-like
- Tenderness
- Achiness
- Stiffness
Symptoms

■ Numbness
■ Burning
■ Tingling
■ Pain (shooting, sharp, cramping, deep, dull, pin/needle pricking)
■ Weakness
■ Muscle wasting
Signs

- Allodynia (pain from stimulus that does not normally evoke pain)
- Hyperalgesia (exaggerated response to a normally painful stimulus)
Summary of Clinical Assessment

- Symptoms
  - Negative: numbness, weakness, gait imbalance
  - Positive: paresthesias, dysesthesias, pain
  - Good days and bad days

- Signs
  - Weakness, atrophy
  - Sensory loss: stocking-glove distribution
  - Reflexes: absent or reduced muscle reflexes
Pain Measure Scales

■ Unidimensional Scales
  - Numeric Rating Scale
  - Visual Analog scale

■ Multidimensional Scale
  - Initial pain assessment too, Brief Pain Inventory (BPI)
  - McGill Pain Questionnaire (MPQ)
Thumb: C6
Middle finger: C7
Little finger: C8
Breast nipple: T4
Umbilicus: T10
Medial knee: L3
Big toe: L4
Little toe: S1

Attention!!!
Evaluation

- Nerve conduction
- Nerve biopsy
- Laboratory testing
- Genetic testing
- CSF analysis
Other Clinical Features Associated with Painful Neuropathy

- Insomnia
- Anxiety
- Depression
- Weight loss
- Decreased quality of life
Trigeminal Neuralgia - Clinical Features

- Predominantly affects V2 and V3 distributions
- Most common in middle-aged women
- Trigger points
- Lancinating pain
- Association with multiple sclerosis
- Normal neurologic examination
Entrapment Neuropathy

- A trapped or pinched nerve at the neck, shoulder, elbow, writs, hip, lower leg or foot
- Carpal tunnel syndrome
- Thoracic outlet syndrome
- Piriformis syndrome
Diabetic Neuropathy – Clinical Features

- 10% of patients have neuropathy at time of diagnosis of diabetes
- 50% develop neuropathy within 25 years of initial diagnosis
- 25% to 33% of neuropathies are associated with pain
- Pain can be superficial (burning, tingling, allodynia), shooting/electric-like, or cramping/aching
Post-Herpetic Neuralgia – Clinical Features

- Pain along course of nerve lasting > 1 month following healing of rash
- Estimated at 9% to 14% (50% at age 60 years and 75% at age 70 years)
- More common in women
- Predilection for thoracic dermatomes and ophthalmic division of trigeminal nerve
- Steady burning/aching pain or paroxysmal jabbing/lancinating pain
Phantom Limb Pain

- Occurs after amputation of an arm/leg
- Exact cause is unknown
- Results when the nerves and the brain send faulty signal to the limb as the circuitry attempts to rewire itself
Comparison of Chronic Regional Pain Syndrome (CRPS) Types

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>CRPS Type 1</th>
<th>CRPS Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitating event</td>
<td>sometimes</td>
<td>yes</td>
</tr>
<tr>
<td>Single peripheral nerve involvement</td>
<td>sometimes</td>
<td>yes</td>
</tr>
<tr>
<td>Physiologic changes in affected limb</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cardinal signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Different skin temperatures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allodynia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>yes</td>
<td>sometimes</td>
</tr>
<tr>
<td>Bone atrophy</td>
<td>yes</td>
<td>no</td>
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# IASP CRPS Diagnostic Criteria

<table>
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<tr>
<th>CRPS I</th>
<th>CRPS II</th>
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<tr>
<td>2-4 of the following with 2, 3, and 4 being mandatory:</td>
<td>All of the following:</td>
</tr>
<tr>
<td>1. The presence of an initiating noxious event, or a cause of immobilization.</td>
<td>1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.</td>
</tr>
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<td>2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.</td>
<td>2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
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<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
<td>3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
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CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain
Management of Neuropathic Pain

The earlier a diagnosis is made, the more opportunities there are to improve patient outcomes.
Goals in the Treatment of Neuropathic Pain

1st goal: >50% pain relief* ...

2nd goals

*in 30–50% can be expected with maximal doses in most patients.
Treatment

- Pharmacologic treatment
- Cognitive behavioral therapy
- Physical and occupation therapy
- Interventional treatment
Pharmacologic Treatment

- Stepwise process to identify which drugs or drug combinations provide the greatest pain relief with fewest side effects
Pharmacologic Agents Affect Pain Differently
FDA APPROVED MANAGEMENT

**First-line**
- SNRIs
  - Amitriptyline, nortriptyline
- SSRIs
  - Venlafaxine, duloxetine
  - Calcium channel α2-δ ligands
    - Gabapentin, pregabalin
- Topical lidocaine

**Second-line**
- Tramadol
  - Opioid, oxycodone, methadone

**Third-line**
- Antidepressant: Bupropion, citalopram, paroxetine
  - Antiepileptic: Topiramate, valproic acid, carbamazepine

**Abbreviations:** SNRIs, Serotonin and norepinephrine reuptake inhibitors; SSRIs, Selective serotonin reuptake inhibitors
# Anti-Neuropathic Drugs

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Major Side Effects</th>
<th>Starting Dose/Maximum Dose</th>
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<tbody>
<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nortriptyline</td>
<td>Inhibition of reuptake of serotonin and/or norepinephrine, block of sodium channels, anticholinergic</td>
<td>Sedation, anticholinergic effects (dry mouth, urinary retention, weight gain)</td>
</tr>
<tr>
<td>Desipramine</td>
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<tr>
<td>Duloxetine</td>
<td>Inhibition of both serotonin and norepinephrine reuptake</td>
<td>Nausea</td>
</tr>
<tr>
<td>Venlafaxine</td>
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<td><strong>Calcium Channel α2–δ Ligands</strong></td>
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<tr>
<td>Gabapentin</td>
<td>Decreases release of glutamate, norepinephrine and substance P, with ligands on α2–δ subunit of voltage-gated calcium channel</td>
<td>Sedation, dizziness, peripheral edema</td>
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<tr>
<td>Pregabalin</td>
<td>Decreases release of glutamate, norepinephrine and substance P, with ligands on α2–δ subunit of voltage-gated calcium channel</td>
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<td><strong>Topical Lidocaine</strong></td>
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<tr>
<td>5% lidocaine patch</td>
<td>Block of sodium channels</td>
<td>Local erythema, rash</td>
</tr>
<tr>
<td><strong>Opioid Agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone, methadone, levorphanol</td>
<td>μ Receptor agonism (oxycodone also causes κ– receptor antagonism)</td>
<td>Nausea/vomiting, constipation, dizziness</td>
</tr>
<tr>
<td>tramadol</td>
<td>μ Receptor agonism, inhibition of norepinephrine and serotonin reuptake</td>
<td>Nausea/vomiting, constipation, dizziness</td>
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World Health Organization (WHO) Analgesic Ladder

- **Mild to moderate pain lasting 3–4 hours**
  - Start with low doses of nonopioid drugs

- **Intermediate pain or pain not well controlled with nonopioid**
  - Combine nonopioid with a low-dose opioid

- **Severe pain**
  - Add a higher dose opioid to the nonopioid, or use a drug that potentiates its analgesic effect like an antihistamine
Interventional Treatments

■ Neural Blockade
  - Sympathetic Blocks for CPRS 1 and II

■ Neurolytic Techniques
  - Alcohol or phenol neurolysis
  - Pulse radiofrequency ablation

■ Neuromodulation
  - Spinal Cord Stimulators
  - Peripheral nerve stimulation
  - Drug Delivery system
Non-Pharmacologic Treatment

- Biofeedback
- Relaxation therapy
- Physical and occupational therapy
- Cognitive/behavioral strategies
  - meditation; guided imagery
- Acupuncture
- Transcutaneous electrical nerve stimulation
Physical and Occupational Therapy

■ Active
  - Improved body mechanics
  - Spine stabilization
  - Stretching & strengthening
  - Aerobic conditioning
  - Aquatics therapy
  - Work hardening
  - Self-directed fitness program
  - MIRROR THERAPY
We have a moral responsibility to address pain and suffering.

And we do have a responsibility not to do harm…