Neuropathic Pain:
Insights Into the Spectrum and Innovative Approaches to Treatment

A CME CD-ROM

Jointly sponsored by the Dannemiller Memorial Educational Foundation and Embryon, Inc.

Supported through an unrestricted educational grant from Pfizer
Neuropathic Pain

- Neuropathic pain is represented by a broad spectrum of patients and is an increasingly significant and costly healthcare problem.
- Neuropathic pain is a chronic condition and often misunderstood and misdiagnosed by physicians.
- In the rehabilitation setting, it is important to address pharmacotherapy and its role in treating the neuropathic pain patient.
- Recent research provides opportunities for more effective management of neuropathic pain patients.
Neuropathic Pain (cont’d)

- Neuropathic pain affects 3.5 to 4 million Americans
- Basic clinical research is revealing new treatment paradigms
- The Joint Commission on Accreditation of Healthcare Organizations has mandated pain as the Fifth Vital Sign
  1. Temperature
  2. Respiration
  3. Blood pressure
  4. Pulse
  5. **Pain**
Decade of Pain Control & Research

Federal Government Recognition

- Implemented by US Congress
  - Began January 1, 2001

- Aims
  - To focus on pain in both the public and private sectors
  - To stimulate research, education, and clinical management

- This is only the second-ever Congressionally declared medical decade (1990s: Decade of the Brain)

Mandatory Physician CME in California

State Government Recognition

- California legislation requires physicians to complete pain management training
  - Treating physicians required to complete 12 hours of CME in pain management and end-of-life care in order to renew their medical license

- Sponsored by Compassion in Dying Federation and Americans for Death With Dignity

- Legislation AB 487 passed October 4, 2001

www.compassionindying.org/releases/AB487.html
Peripheral and Central Mechanisms of Neuropathic Pain

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Director, Division of Pain Medicine/Hospice
Greater Lehigh Valley Health Network
Allentown, PA
Normal CNS Function

Excitation

Glutamate, Aspartate

Inhibition

GABA
Abnormal Excitation

Glutamate, Aspartate → Inhibition

Excitation

GABA
Nerve Injury Leads to Peripheral and Central Changes

Nerve Injury → Peripheral Changes → Neuropathic Pain → Central Changes
Mediators Released After Peripheral Tissue Injury
### Fiber Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Function</th>
<th>Diameter (μm)</th>
<th>Velocity (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Pain, mechanical stimuli</td>
<td>1 (no myelin)</td>
<td>0.2-1.5</td>
</tr>
<tr>
<td>B</td>
<td>Preganglionic/autonomic</td>
<td>1</td>
<td>3-14</td>
</tr>
<tr>
<td>Aδ</td>
<td>Pain, mechanical, thermal</td>
<td>1</td>
<td>5-15</td>
</tr>
<tr>
<td>Aγ</td>
<td>Touch, muscle tone</td>
<td>4</td>
<td>15-40</td>
</tr>
<tr>
<td>Aβ</td>
<td>Touch, proprioception</td>
<td>8</td>
<td>40-70</td>
</tr>
<tr>
<td>Aα</td>
<td>Motor</td>
<td>13</td>
<td>70-120</td>
</tr>
</tbody>
</table>
Effect of Nerve Injury at the Spinal Cord

Afferent fibers
Peripheral sensitization

Spinal cord

Neuroplasticity

Central sensitization

Alteration of modulatory systems

Nerve injury
Ectopic discharges
C fiber
A beta fiber
Ectopic discharges

Phenotypical changes

Mechanisms of Neuropathic Pain

Mechanisms of Neuropathic Pain (Cont’d)

Primary afferent C fiber → GLU → NKA → SP → NK Receptor

AMP A

Prime NMDA

Ca^{2+}

Mg^{2+}

Na^{+}
Mechanisms of Neuropathic Pain (Cont’d)

\[ \text{Ca}^{2+} \]

**PLC** → Arachidonic acid, diacylglycerol

**PKC, AC** → Phosphorylates NMDA receptor

**NOS** → cAMP

**C-fos** → Increased presynaptic activity

Long-term cellular changes

PLC = phospholipase C; PKC = protein kinase C; AC = adenyl cyclase; NOS = nitric oxide synthase; cAMP = cyclic adenosine monophosphate.
Altered Sodium Channels and Central Sensitization

Afferent fibers

- Nerve injury
- C fiber
- A beta fiber

Ectopic discharges

Spinal cord

- Na+ modulators
- Neuroplasticity
- Central sensitization
- Alteration of modulatory systems

Phenotypical changes

Peripheral and Central Mechanisms

- **Peripheral**
  - Sensitization of peripheral neurons
  - Collateral sprouting of A fibers
  - Increased activity of damaged axons and their sprouts

- **Central**
  - Central sensitization
  - Reorganization of synaptic connectivity
  - Disinhibition
Hyperalgesia

- Increased response to a painful stimulus
  - Pinprick pain
  - Heat
Peripheral Sensitization

Results from antidromic activation, neurogenic inflammation, or exposure to molecules such as nerve growth factor (NGF)

Innocuous stimulus  Mechanical and thermal hyperalgesia  Pain sensation

Central Sensitization

**Normal sensory function:** $\alpha$ fiber activation by low-threshold stimuli is unable to activate dorsal horn pathways

![Diagram showing normal sensory function]

**Increased nociceptor drive leads to central sensitization of dorsal horn neurons.** $\alpha$ fiber input is now sufficient to activate spinal cord pain pathways.

![Diagram showing central sensitization]

**Brush-Evoked Mechanical Hyperalgesia**

Allodynia

- The interpretation of a non-painful stimulus as being painful
- The result of a qualitative change in the interpretation of a stimulus
  - Dynamic Aβ fiber mediated
  - Static C fiber mediated
A Fiber Sprouting

Normal terminations of primary afferents in the dorsal horn

After nerve injury, C fiber terminals atrophy and A fiber terminals sprout into the superficial dorsal horn

Hyperpathia

- An exaggerated and prolonged response to a painful stimulus
- A quantitative change in the interpretation of a stimulus
Disinhibition

Excitability in dorsal horn neurons is determined by a balance between excitatory inputs from primary afferents and inhibitory inputs (local and descending).

Nerve injury reduces inhibitory input, increasing excitability in dorsal horn neurons; Primary afferent inputs now evoke a much greater response, and dorsal neurons may fire spontaneously.

Innocuous or noxious stimulus

Excitatory Synapse

Inhibitory Synapse

Exaggerated pain response

Spontaneous Stimuli

- Peripheral/DRG sodium channel function
  - Sprouting of sympathetic nerve terminals

- Paresthesia
  - Nonpainful

- Dysesthesia
  - Painful or unpleasant

DRG = dorsal root ganglia.
Stimulus-independent Pain

Normal sensory function

Receptor

To brain
Pain sensation

Nociceptor

Dorsal horn

Noxious stimulus

After nerve injury, spontaneous firing along the axon

No stimulus

Na+

After nerve injury, spontaneous firing of dorsal horn neurons in the spinal cord

No stimulus

Functional Cascade of Neuropathic Pain

Genetics
Initiating event
Age
Critical modulators

Genetics
Age
Structural/functional changes
Neuropathic pain

Disease modification (future)

Symptomatic treatment (current)

Restoring Balance

Increase inhibition

Excitation

Inhibition

Reduce excitation
Clinical Manifestations of Neuropathic Pain in the Rehabilitation Setting

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Pain! Which Pain?

**Inflammatory pain** (e.g., rheumatoid arthritis)
- Nociceptor activation
- Severity of pain = severity of disease

*Physiology of pain*

**Chronic neuropathic pain** (e.g., post-stroke central pain)
- Nervous system is changed
- Severity of pain = degree of neuroplasticity

*Pathophysicsiology of pain*
Pain Symptoms

SPONTANEOUS PAIN: "BEING RIPPED OPEN FROM INSIDE OUT"

Aβ DEPENDENT MECHANO-ALLODYニア

"NAGGING" PAIN
MOVEMENT OR VIBRATION PRODUCES ELECTRIC SHOCK-LIKE PAIN

ATROPHIC HYPERPIGMENTED Aβ DEPENDENT MECHANO-ALLODYニア PALPATION EVOKES SEVERE, RADIATING PAIN

SPONTANEOUS, STABBING

Neuropathic Pain

Syndromes (common examples)

- Painful diabetic neuropathy
- Postherpetic neuralgia
- Traumatic neuralgia — complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), post-amputation
- Radiculopathies (cervical, thoracic, lumbosacral)
- Cancer-related neuropathic pain
- Trigeminal neuralgia
- Central pain syndrome — spinal cord, brainstem, brain (thermonociceptive pathways and relays)
Prevalence of Neuropathic Pain in the US

*Estimates are believed to be conservative.
†Assumes 1 in every 10 patients with lower back pain has a component of neuropathic pain.
PDN=painful diabetic neuropathy; PHN=postherpetic neuralgia.
Neuropathic Pain

**Pattern**

- Peripheral examples
  - Mononeuropathy
  - Mononeuropathy multiplex
  - Brachial plexopathy
  - Lumbosacral plexopathy
  - Monoradiculopathy
  - Polyradiculopathy
  - Polyradiculoneuropathy
Neuropathic Pain (Cont’d)

*Pattern* (cont’d)

- Central examples
  - Hemicord (Brown-Sequard) syndrome
  - Complete transection = transverse myelitis
  - Disseminated myelopathy
  - Brainstem syndromes
  - Thalamic lesions
  - Cortical lesions
Neuropathic Pain (cont’d)

Pathologic mechanisms

- Injury
- Compression
- Inflammation
- Ischemia
- Infections
- Demyelination
- Axonopathies
- Metabolic/toxic
- Neoplasm
Complexity of Neuropathic Pain

*Sensory abnormalities*

- Positive sensory phenomena
  - Ongoing spontaneous pain
  - Spontaneous paroxysms
  - Hyperalgesia

- Negative sensory phenomena
  - Sensory deficits at varying degrees to any or all sensory modalities (light touch, pain...)
Complexity of Neuropathic Pain
(cont’d)

Motor abnormalities

• Negative motor phenomena
  - Weakness
  - Clumsiness
  - Fatigue

• Positive motor phenomena
  - Tremor
  - Dyskinesiae
  - Ataxia
  - Dystonia
Neuropathic Pain (cont’d)

Rehabilitation medicine-related pain syndromes (cont’d.)

- Spinal disorders
  - Spinal segmental instability
  - Radiculopathy
  - Spinal stenosis

- Spinal cord injury
  - Instability-related
  - Transitional zone-related pain
  - Central pain

- Central post-stroke and other pain and dysesthesia syndromes
Neuropathic Pain Scales

**Galer and Jensen 1997**
- Quantitative
- Validated in clinical trials

**The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale**
- Qualitative
- Relies on physical exam as well

Clinical Importance of Changes in Chronic Pain Intensity

- A consistent and close relationship between changes in pain intensity NRS and PGIC was demonstrated
  - Pain can be reliably measured with easy-to-use validated rating scales

- On average, a reduction of \(\approx 2\) points or \(\approx 30\%\) on the pain intensity NRS represented a clinically important improvement as determined by PGIC assessment
  - Modest changes in pain rating scale scores (2 to 3 points) are associated with clinically meaningful changes in patient and physician impressions of overall improvement

NRS=numerical rating scale; PGIC=Patient Global Impression of Change.
## Pain Assessment

<table>
<thead>
<tr>
<th>Items/Issues</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>When and how did the pain start?</td>
</tr>
<tr>
<td>Location(s)/site(s)</td>
<td>Where is (are) pain(s) located?</td>
</tr>
<tr>
<td>Temporal profile</td>
<td>What has happened since onset?</td>
</tr>
<tr>
<td>Characteristics/quality of pain(s)</td>
<td>Describe the pain.</td>
</tr>
<tr>
<td>Severity</td>
<td>How severe is the pain?</td>
</tr>
<tr>
<td>Unpleasantness/distress</td>
<td>How unpleasant is the pain?</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Are there any other symptoms, such as numbness, weakness, bowel/bladder dysfunction, or insomnia?</td>
</tr>
<tr>
<td>Psychological factors</td>
<td>Does patient suffer from depression? Anxiety?</td>
</tr>
<tr>
<td>Aggravating factors</td>
<td>What makes the pain(s) worse?</td>
</tr>
<tr>
<td>Alleviating factors</td>
<td>What makes the pain(s) better?</td>
</tr>
<tr>
<td>Impact on function and activities</td>
<td>How are work and daily activities affected?</td>
</tr>
<tr>
<td></td>
<td>Is the patient active in recreational pursuits?</td>
</tr>
<tr>
<td>Response to past treatments</td>
<td>What prior treatments has patient received?</td>
</tr>
<tr>
<td>Habits</td>
<td>Does patient smoke? Drink? Use illegal drugs?</td>
</tr>
<tr>
<td></td>
<td>If yes, how much and how often?</td>
</tr>
<tr>
<td>Coping skills</td>
<td>How is patient coping with pain?</td>
</tr>
</tbody>
</table>
Neuropathic Pain

Rehabilitation medicine-related pain syndromes

- Traumatic neuropathies
  - Causalgia
  - CRPS/RSD

- Amputation
  - Stump pain
  - Phantom pain
Neuropathic Pain

Pain Assessment and Evaluation

- Establishment of neuropathic pain = H&P
- Differentiation from other sources and mechanisms of pain:
  - Bony and ligamentous pain = instability, irritation
  - Secondary myofascial pain syndromes
  - Referred pain from distant and visceral sources
Pain Intensity and Functional Interference

Functional impact is significantly correlated with pain severity ($P<0.0001$)

1 - 2

1. Enjoyment of life
2. Overall mood

3 - 4

3. Work
4. Sleep
5. Enjoyment of life
6. Overall mood

5 - 6

5. Relations with others
6. Ability to walk
7. Work
8. Sleep
9. Enjoyment of life
10. Overall mood

8 - 10

8. General activity
9. Relations with others
10. Ability to walk
11. Work
12. Sleep
13. Enjoyment of life
14. Overall mood

An Interdisciplinary Approach to Neuropathic Pain

VOC  PT  OT

PATIENT

RT  PSYCH  MD
Conclusions

- Determination of mechanisms - neuropathic vs inflammatory
- Specific pain diagnosis should lead to specific pain therapy
Approaches to the Management of Neuropathic Pain: Targeting the Putative Mechanisms

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Program Chair
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Northwestern University
Director, Center for Pain Studies
Rehabilitation Institute of Chicago
Chicago, IL
Treatment of Neuropathic Pain

- Targeting the underlying cause
- Targeting pain characteristics
- Targeting putative pathophysiological mechanisms
Bio-psycho-social Disease

VOC  PT  OT

PATIENT

RT  PSYCH  MD
Nonpharmacologic Treatment

- Thermal Biofeedback
- Heat
- Herbal Medicine
- Progressive Muscle Relaxation (PMR)
- Bloodletting
- Trephining
- Acupuncture
- Diaphragmatic Breathing
- Occlusal Adjustment
- Placebo
- TENS
- BIOMECHANICAL FEEDBACK
- YOGA
- Physical Therapy
- Mesmerism
- Relaxation
- Galvanic Skin Response (GSR)
- Electromyography (EMG) Biofeedback
- Hypnosis
- Autogenics
- Chiropractic Adjustment
- Ice
- Occlusal Splint
Patient with trigeminal postherpetic neuralgia treated with:

- Alcohol injection into supra-orbital nerve
- Division of the sensory root
- Alcohol injection into trigeminal ganglion
- Stellate ganglion block
- Electroconvulsive therapy
- Extirpation of contralateral, then ipsilateral, sensory cortex
- Prefrontal lobotomy

Neuropathic Pain Agents and Their Actions

**Brain**
- NE
- Serotonin
- Endogenous opiates
- Tricyclic Antidepressants
- Selective Serotonin Reuptake Inhibitors

**Spinal Cord**
- Na⁺
- Ca⁺⁺ + channels: Gabapentin, Oxcarbazepine
- NMDA antagonists: Ketamine, Dextromethorphan, Topiramate

**PNS**
- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Mexiletine
- Lidocaine
- Lamotrigine, Topiramate
## Pharmacologic Management of Neuropathic Pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, imipramine, desipramine, nortriptyline</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, oxcarbazepine, clonazepam, gabapentin, lamotrigine, phenytoin, valproic acid, topiramate</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Lidocaine, mexiletine</td>
</tr>
<tr>
<td>Topical formulations</td>
<td>Capsaicin, lidocaine, aspirin</td>
</tr>
<tr>
<td>Others</td>
<td>Tramadol, NMDA antagonists, clonidine, opioids</td>
</tr>
</tbody>
</table>
Clinical Importance of Changes in Chronic Pain Intensity

CLBP = chronic low-back pain; FIB = fibromyalgia; OA = osteoarthritis; PDN = painful diabetic neuropathy; PHN = postherpetic neuralgia; PI-NRS = Pain Intensity-Numerical Rating Scale.

## Nonsteroidal Anti-inflammatory Agents (NSAIDs) by Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acids</td>
<td>Choline magnesium</td>
<td>Trilisate®</td>
</tr>
<tr>
<td></td>
<td>Trisalicylate</td>
<td></td>
</tr>
<tr>
<td>Indoleacetic acids</td>
<td>Sulindac</td>
<td>Clinoril®</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>Indocin®</td>
</tr>
<tr>
<td></td>
<td>Etodolac</td>
<td>Lodine®</td>
</tr>
<tr>
<td>Pyrrolacetic acids</td>
<td>Tolmetin sodium</td>
<td>Tolectin®</td>
</tr>
<tr>
<td></td>
<td>Ketorolac tromethamine</td>
<td>Toradol®</td>
</tr>
<tr>
<td>Propionic acids</td>
<td>Ketoprofen</td>
<td>Orudis®, Oruvail®</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Motrin®</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>Naprosyn®</td>
</tr>
<tr>
<td>Naphthylalkanones</td>
<td>Nabumetone</td>
<td>Relafen®</td>
</tr>
</tbody>
</table>
Steroids

Adrenocorticosteroids
Prednisone high dose, rapid taper
IE: 80 mg x 3 days, 60 x 3,
40 x 3, 20 x 3, 10 x 3, 5 x 3
Not for chronic use
Chemical Structure of Tricyclic Antidepressants (TCAs)

Tertiary amines

- Imipramine
- Amitriptyline

Secondary amines

- Nortriptyline
- Desipramine
# TCAs in Postherpetic Neuralgia

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Watson et al (1982)</strong></td>
<td>24</td>
<td>A: 67%</td>
</tr>
<tr>
<td>Amitriptyline vs placebo</td>
<td></td>
<td>P: 5%</td>
</tr>
<tr>
<td><strong>Max et al (1988)</strong></td>
<td>24</td>
<td>A: 47%</td>
</tr>
<tr>
<td>Amitriptyline vs placebo</td>
<td></td>
<td>P: 16%</td>
</tr>
<tr>
<td><strong>Kishore-Kumar et al (1980)</strong></td>
<td>19</td>
<td>D: 63%</td>
</tr>
<tr>
<td>Desipramine vs placebo</td>
<td></td>
<td>P: 11%</td>
</tr>
<tr>
<td><strong>Watson et al (1992)</strong></td>
<td>32</td>
<td>A: 44%</td>
</tr>
<tr>
<td>Amitriptyline vs maprotiline</td>
<td></td>
<td>M: 18%</td>
</tr>
<tr>
<td><strong>Watson and Evans (1985)</strong></td>
<td>15</td>
<td>A: 60%</td>
</tr>
<tr>
<td>Amitriptyline vs zimeldine (SSRI)</td>
<td></td>
<td>Z: 7%</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor.
# Common Side Effects Associated with TCAs

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Anticholinergic effects</th>
<th>Hypotension</th>
<th>Cardiac effects</th>
<th>Seizures</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0/+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

0/+ = minimal; += mild; ++ = moderate; +++ = moderately severe.

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A comparative trial showed that paroxetine led to significantly better pain relief than placebo in patients with PDN.

Although paroxetine was better tolerated, it had significantly less efficacy compared with imipramine.

A randomized, double-blind, crossover design trial showed that citalopram induced slight relief of pain for patients with PDN.
Venlafaxine and PDN

- Randomized, placebo-controlled trial of 224 patients with PDN and no depression
- Venlafaxine (VLF) XR administered at 75 mg and at 150 mg to 225 mg for up to 6 weeks
- Venlafaxine (150 mg to 225 mg) resulted in significantly better pain relief at weeks 2 to 6 and significantly decreased pain intensity at weeks 4 and 6
- At week 6, 56%, 39%, and 35% of patients on VLF 150 mg to 225 mg, VLF 75 mg, and placebo, respectively, reported significantly reduced pain intensity

Kunz N. et al. Presented at the 60th annual meeting of the ADA, San Antonio, TX, 2000.
Opioid Analgesics: Sites of Action

Efficacy of Controlled-release Oxycodone in Postherpetic Neuralgia

**VAS pain intensity (0-100 mm)**

- **Steady pain**
  - Placebo: 55
  - CR oxycodone: 34*

- **Brief pain**
  - Placebo: 42
  - CR oxycodone: 22*

- **Alldynia**
  - Placebo: 50
  - CR oxycodone: 32†

*P=0.0001; †P=0.0004.
NMDA Antagonists and PDN

- Animal and pilot data suggest that NMDA receptor blockade may alleviate neuropathic pain
- Significant side effects from NMDA antagonists (MK 801, ketamine, phencyclidine)
- High doses of low-affinity, noncompetitive, NMDA-receptor antagonist (dextromethorphan, remacemide) may have a better therapeutic ratio

NMDA = N-methyl-D-aspartate.
Oral Dextromethorphan and PDN

- Randomized, placebo-controlled, 2-period, crossover design trial (1-week baseline, two 6-week Rx periods, 1-week washout period)
- Dextromethorphan started at 120 mg/day and titrated to a maximum of 960 mg/day (by 30 to 60 mg every 3 days)
- 14 patients (mean dose 381 mg); dextromethorphan reduced pain by 24% compared with placebo
- Most common AEs were sedation, dizziness, and lightheadedness

Topical Treatments for Neuropathic Pain

Capsaicin

Lidocaine patch 5%
Capsaicin and PDN

- Multicenter, double-blind, vehicle-controlled trial
- 252 patients on topical 0.075% capsaicin vs vehicle cream applied 4x daily for 8 weeks
- Statistically significant improvement in pain favoring capsaicin (69.5% vs 53.4%), pain intensity (38.1% vs 27.4%), and pain relief (58.4% vs 45.3%)
- Capsaicin caused transient burning, sneezing, and coughing
Topical Medications

Capsaicin
- Inconsistent trial results; potential burning upon application

EMLA Cream
- May help some patients with allodynia

Clonidine gel
- Pilot studies suggest efficacy; controlled trial in progress

Unstudied custom compounds
- Doxepin, other TCAs, gabapentin, opioids, ketamine, guanethidine
### Anticonvulsant Drugs and Neuropathic Pain

<table>
<thead>
<tr>
<th>First-generation</th>
<th>Second-generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine(^A)</td>
<td>Gabapentin(^A)</td>
</tr>
<tr>
<td>Divalproex sodium(^B)</td>
<td>Lamotrigine(^A)</td>
</tr>
<tr>
<td>Phenytoin(^A)</td>
<td>Levetiracetam(^B)</td>
</tr>
<tr>
<td>Valproic acid(^B)</td>
<td>Oxcarbazepine(^A)</td>
</tr>
<tr>
<td>Clonazepam(^B)</td>
<td>Tiagabine(^B)</td>
</tr>
<tr>
<td>Phenobarbital(^B)</td>
<td>Topiramate(^B)</td>
</tr>
<tr>
<td>Zonisamide(^B)</td>
<td></td>
</tr>
</tbody>
</table>

\(^A\) Published randomized controlled trials.
\(^B\) Clinical anecdotes and/or published case series.
Anticonvulsants: Mechanisms of Action

Voltage-gated sodium channel

Open

\[ \text{Na}^+ \]

\[ \text{A} \]

Phenytoin
Carbamazepine
Oxcarbazepine

Inactivated

\[ \text{Na}^+ \]

\[ \text{A} \]

Topiramate
Lamotrigine
Zonisamide

A = activation gate;
I = inactivation gate.

Anticonvulsants: Mechanisms of Action (cont’d)

Voltage-gated calcium channel

Subtypes
- L-type
- T-type
- N-type*
- P-type*

Gabapentin
Oxcarbazepine

* Found in neuronal tissue.

Mechanisms of Action of Phenytoin

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- May inhibit somatostatin release

Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. 
Phenytoin in PDN

Conflicting data

- **Saudek et al, 1977**
  - Double-blind, placebo-controlled, crossover trial of 4 weeks; 12 patients
  - Pain relief on linear analog scale
  - No significant difference between phenytoin and placebo

- **Chadda and Mathur, 1978**
  - Double-blind, placebo-controlled, crossover trial of 5 weeks; 38 patients
  - Categorical scale of improvement
  - Significant improvement with phenytoin

Pharmacologic Properties of First-generation Anticonvulsants

Carbamazepine

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- May inhibit release of somatostatin
- Some calcium antagonistic effect

McNamara JO. In: Goodman and Gilman’s The Pharmacological Basis of Therapeutics. 9th ed. 1996:461-486.
Carbamazepine (CBZ) in PDN

- Double-blind, placebo-controlled, crossover trial of 6 weeks (three 2-week periods); 30 patients
- Pain relief on a categorical scale
- 63% of patients on carbamazepine had moderate to complete relief vs 20% of patients on placebo (P<.05)
- Median carbamazepine dose 600 mg

CBZ in PDN (con'd)

Patients with pain relief on treatment (%)

Patients with pain relief on placebo (%)

- Antidepressants
- Carbamazepine

Mechanisms of Action of Oxcarbazepine (OXC)

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- Modulates high-threshold N- and P-type calcium channels
- Reduces glutamatergic transmission
OXC vs CBZ in Trigeminal Neuralgia (TN)

Results

<table>
<thead>
<tr>
<th></th>
<th>OXC</th>
<th>CBZ</th>
</tr>
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<tbody>
<tr>
<td>Pain during eating</td>
<td>61</td>
<td>65</td>
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<tr>
<td>Global assessment</td>
<td>81</td>
<td>82</td>
</tr>
</tbody>
</table>
Pharmacologic Properties of Second-generation Anticonvulsants

Gabapentin

- Increases GABA in brain, possibly by enhancing rate of synthesis from glutamate
- Binds to alpha 2 delta subunit of voltage dependent Ca+ channel
- Inhibits sodium currents by mechanism distinct from phenytoin and carbamazepine
- Inhibits branched-chain amino acid transferase, possibly reducing glutamate concentration
- No effect on GABA_A or GABA_B receptors

### Gabapentin in Neuropathic Pain
**Double-blind, placebo-controlled studies**

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Indication</th>
<th>N</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Results</th>
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<tbody>
<tr>
<td>Backonja 1998</td>
<td>DPN</td>
<td>165</td>
<td>900-3600</td>
<td>8</td>
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<tr>
<td>Rowbotham 1998</td>
<td>PHN</td>
<td>225</td>
<td>1200-3600</td>
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<tr>
<td>Rice 2001</td>
<td>PHN</td>
<td>334</td>
<td>1800 or 2400</td>
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<tr>
<td>Serpell In Press</td>
<td>Neuropathic pain</td>
<td>305</td>
<td>900-2400</td>
<td>8</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Gabapentin in PDN

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel design trial in 165 patients titrated up to 3600 mg/day

- Average daily pain score dropped from 6.4 to 3.9 on gabapentin compared with a drop from 6.5 to 5.1 for placebo (P<.001)

- Most common adverse events of GBP were dizziness and somnolence

Gabapentin in Postherpetic Neuralgia

- Multicenter, randomized, double-blind, 8-week, placebo-controlled, parallel-design trial in 229 patients titrated up to 3600 mg/day

- Average daily pain score dropped from 6.3 to 4.2 on gabapentin compared with a drop from 6.5 to 6.0 for placebo (P<.001)

- Somnolence, dizziness, ataxia, peripheral edema, and infection more frequent in gabapentin group

Mechanisms of Action of Topiramate (TPM)

- Blocks voltage-gated Na+ channels
- Blocks kainate and AMPA subtypes of the glutamate receptor
- Enhances GABA_A receptor actions by interaction with a nonbenzodiazepine receptor

Topiramate (TPM) in PDN

- Double-blind, placebo-controlled (2:1) trial of 13 weeks duration in 27 patients
- TPM titrated over 9 weeks up to 400 mg/day
- Average daily pain score dropped from 6.9 to 4.1 on TPM compared with an increase from 6.5 to 7.0 for placebo (P=.007)
- 5/18 patients (28%) on TPM vs 1/9 patients (11%) on placebo exited because of intolerable adverse events

Edwards KR et al. Presented at the 18th Annual Scientific Meeting of the American Pain Society; October 21-24, 1999; Fort Lauderdale, FL.
Mechanisms of Action of Lamotrigine (LMG)

- Slows recovery rate of voltage-activated Na+ channels, limiting repetitive firing
- Inhibits neurotransmitter release (glutamate, aspartate, acetylcholine, GABA) mediated by sodium influx

# LMG in Neuropathic Pain

## Double-blind, placebo-controlled studies

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Indication</th>
<th>N</th>
<th>Dose (mg/day)</th>
<th>Duration</th>
<th>Results</th>
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<td>McCleane 1999</td>
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<td>Central post stroke pain</td>
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<td>Mechanisms of Action</td>
<td>Drugs</td>
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<td>Na⁺ channel blocker</td>
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<td>Oxcarbazepine</td>
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<td>Vigabatrin</td>
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<td>Valproate</td>
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<td>Glutamate metabolism</td>
<td>Gabapentin</td>
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"RATIONAL POLYPHARMACY"
“Today’s dogma will be tomorrow’s heresy...”

D.J. Dalessio
Neuropathic Pain: A Brief Recap

- Neuropathic pain affects 3.5 to 4 million Americans
- Basic clinical research is revealing new treatment paradigms
- The Joint Commission on Accreditation of Healthcare Organizations has mandated pain as the Fifth Vital Sign
  1. Temperature
  2. Respiration
  3. Blood pressure
  4. Pulse
  5. *Pain*
Neuropathic Pain: A Brief Recap

- The very nature of neuropathic pain makes it difficult to diagnose. Therefore, it is often misdiagnosed, and is underreported.

- Chronic pain is a combination of inflammatory and neuropathic mechanisms.

- Treating only the inflammatory (nociceptive) component will be ineffective.
Conclusion: Treating the Patient to Goal

- The triad of pain - mood disorders and functional impairment, including sleep disorders, must be addressed.

- Modest improvements in pain scores reported by a patient can mean improved quality of life - the ultimate goal of treatment.
Conclusion: Comprehensive Management of Neuropathic Pain

- No one agent is approved
- Medications are often prescribed without careful consideration of intended effect
- Patients are often sub-optimally treated
- Rational polytherapy may be necessary
Conclusion: The New Treatment Paradigm

- As a result of the shifting treatment paradigm from a mechanism- to an evidence-based approach, clinicians are diagnosing patients according to specific signs and symptoms.

- The patient and clinician can develop a treatment strategy specifically targeted to the individual patient’s signs and symptoms.