Neuropathic Pain: New Strategies to Improve Clinical Outcome

Systematic Management of Painful Neurological Disorders of HIV

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IASP Definition of Pain

“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”

Common Types of HIV Pain

- Pain Related to HIV Infection
- Pain Related to HIV Treatment
- Pain Unrelated to HIV

Acute vs Chronic Pain

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Generally known</td>
<td>Often unknown</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>Short, well-characterized</td>
<td>Persists after healing, ≥3 months</td>
</tr>
<tr>
<td>Treatment approach</td>
<td>Underlying disease</td>
<td>Underlying disease and pain disorder</td>
</tr>
</tbody>
</table>

Effects of Chronic Pain on the Patient

<table>
<thead>
<tr>
<th>Physical Functioning</th>
<th>Psychological Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to perform activities of daily living</td>
<td>Depression</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Anger</td>
</tr>
<tr>
<td></td>
<td>Loss of self-esteem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social Consequences</th>
<th>Societal Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationships with family and friends</td>
<td>Healthcare costs</td>
</tr>
<tr>
<td>Intimacy/sexual activity</td>
<td>Disability</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Lost workdays</td>
</tr>
</tbody>
</table>

Nociceptive vs Neuropathic Pain

- Nociceptive Pain
  - (Inflammatory?)
  - Caused by activity in neural pathways in response to potentially tissue-damaging stimuli
- Mixed Type
  - Caused by a combination of both primary injury and secondary effects
- Neuropathic Pain
  - Initiated or caused by primary lesion or dysfunction in the nervous system

*Complex regional pain syndrome.
**Neuropathic Pain: New Strategies to Improve Clinical Outcome**

### Diagnosis: Identifying the Type of Neuropathy

<table>
<thead>
<tr>
<th>Mononeuropathy</th>
<th>Mononeuropathy Multiplex</th>
<th>Plexopathy</th>
<th>Polyneuropathy</th>
</tr>
</thead>
</table>

### Possible Descriptions of Neuropathic Pain

- Sensations
  - burning
  - paresthetic
  - paroxysmal
  - lancinating
  - electriclike
  - raw skin
  - shooting
  - deep, dull, bonelike ache

- Cardinal signs/symptoms
  - allodynia: pain from a stimulus that does not normally evoke pain
  - thermal
  - mechanical
  - hyperalgesia: exaggerated response to a normally painful stimulus

### Neuropathic Pain: Issues and Challenges

- Common type of pain
  - 25% to 50% of all pain clinic visits
- Underassessment and under-treatment
- Interpatient variability in response to treatment
- Patient not believed
- Complex pathophysiology

### Physiology of Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

### Pathophysiology of Neuropathic Pain

- Chemical excitation of nonnociceptors
- Recruitment of nerves outside of site of injury
- Excitotoxicity
- Sodium channels
- Ectopic discharge
- Deafferentation
- Central sensitization
  - maintained by peripheral input
- Sympathetic involvement
- Antidromic neurogenic inflammation

### Multiple Pathophysiologies May Be Involved in Neuropathic Pain

- More than one mechanism of action likely involved in neuropathic pain
- Neuropathic pain may result from abnormal peripheral nerve function and neural processing of impulses due to abnormal neuronal receptor and mediator activity
- Combination of medications may be needed to manage pain: topicals (lidocaine patch 5%/capsaicin), anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioids
- In the future, the ability to determine the relationship between the pathophysiology and symptoms/signs may help target therapy
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Herpes Zoster (Thoracic Dermatome)

Percentages of Herpes Zoster Patients With Persistent Pain

- 0 19 29 39 49 59 69 ≥70
- 0 10 20 30 40 50 60 70 80

Adapted from DeMorgas JM, Kierland RR. Arch Dermatol. 1957;75:193-196.

What Are the Goals of Clinical Assessment?

- Achieve diagnosis of pain
- Identify underlying causes of neuropathy
- Identify comorbid conditions
- Evaluate psychosocial factors
- Evaluate functional status (activity levels)
- Set goals
- Develop a targeted treatment plan
- Determine when to refer to specialist or multidisciplinary team (pain clinic)

Assessing the Patient Who Has Pain

- Onset and duration
- Location/distribution
- Quality
- Intensity
- Aggravating/relieving factors
- Associated features or secondary signs/symptoms
- Associated factors
  - mood/emotional distress
  - functional activities
- Treatment response

Pain Assessment Scales

<table>
<thead>
<tr>
<th>Verbal Pain Intensity Scale</th>
<th>Visual Analog Scale</th>
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</thead>
<tbody>
<tr>
<td>No pain</td>
<td>Mild pain</td>
</tr>
<tr>
<td>No pain</td>
<td>No pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>0–10 Numeric Pain Intensity Scale</th>
<th>“Faces” Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>


Neuropathic Pain Assessment Tools

- Neuropathic Pain Scale (NPS)¹
  - Expert opinion; 10 items
  - Distinctions:
    - Deep and surface pain
    - Sensation and unpleasantness
- Neuropathic Pain Questionnaire (NPQ)²
  - Empirically derived; 10 items
- Neuropathic Pain Symptom Inventory (NPSI)³
  - Empirically derived; 12 items
  - Distinctions:
    - spontaneous pain, evoked pain, paroxysms, paresthesiae

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Clinical Assessment:
Neurologic History

- Symptoms
- Onset
- Etiologic factors
  - diabetes mellitus (undiagnosed)
  - alcohol
  - vitamin deficiencies (B₁₂, thiamine, etc)
  - hereditary
  - neurotoxicity (environmental, iatrogenic)
  - trauma/structural lesions (herniated nucleus pulposus, carpal tunnel syndrome)

Clinical Assessment:
Neurologic Examination

- Sensory examination
  - helps confirm neuropathic pain and distribution
- Sensory elements
  - sensory deficits: eg, touch, pin, temperature, vibration
  - allodynia: light touch
  - hyperalgesia: single or multiple pinpricks

Clinical Assessment:
Neurologic Examination (cont)

- Motor
  - muscle bulk/tone (atrophy/flaccidity)
  - muscle strength
  - coordination
  - gait
- Autonomic
  - limb temperature
  - sweating
  - hair and nail growth
  - skin color changes

Clinical Assessment:
Psychosocial History

- Current psychiatric symptoms
- History of addictive disease
- Change in social function
  - work
  - family and relationships
  - recreation
- Medical-legal status

Diagnostic Studies and Limitations

Studies
- Blood studies
- X-ray, CT, MRI
- Electromyography (EMG)
- Nerve conduction velocity (NCV)
- Quantitative sensory testing (QST)
- Epidermal skin biopsy

Limitations of EMG/NCV
- Insensitive in acute injury
- Normal result does not rule out neuropathic pain
- Cannot assess function of small-fiber nerves involved in most neuropathic pain

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“Discouraging data on the antidepressant.”

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Neuropathic Pain: Approach to Treatment

- Diagnosis
- Treat underlying condition/symptomatic treatment
- Reduce pain
- Prevention (if applicable)
- Improve physical functioning
- Reduce psychological distress
- Improve overall quality of life


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Multidisciplinary Treatment of Neuropathic Pain

- Pharmacotherapy and other medical/surgical care with appropriate medicine reorganization
- Restorative care including active physical and occupational therapy
- Psychological counseling utilizing cognitive-behavioral pain management strategies

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Pain Treatment Continuum

Least invasive: Psychological/physical approaches
- Topical medications
- Oral medications*
- Injections*
- Interventional techniques*

Most invasive: Continuum not related to efficacy

*Consider referral if previous treatments were unsuccessful.

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Nonpharmacologic Options

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

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Pharmacotherapeutic Considerations: Setting Priorities

- Efficacy
  - clinical trial data
  - clinical experience
- Safety/tolerability
- Ease of use
  - dosing
  - titration
  - drug-drug interactions
  - patient acceptability
- Cost

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NATIONAL INITIATIVE ON PAIN CONTROL™
### Pharmacotherapy Guidelines

1. Medication must result in:
   - Significant pain relief
   - Tolerable side effects
   - Function

2. Both physician & patient must realize significant individual variability

3. Slow titration until either:
   - a) Significant pain relief
   - b) Intolerable side effects
   - c) “Toxic serum level”

4. Educate the patient

### Pharmacotherapy

- NSAIDs/Cox-2
- Acetaminophen
- Antidepressants
- Anticonvulsants
- Opioids
- Oral local anesthetics
- Alpha adrenergic agents
- Neuroleptics
- NMDA receptor antagonists
- Muscle relaxants
- Topical analgesics
- Emerging Agents
### Pharmacologic Treatment Options

- Agents with consistent efficacy demonstrated in multiple, randomized, controlled trials for neuropathic pain
  - lidocaine patch 5% (topical analgesic)
  - gabapentin (anticonvulsant)
  - nortriptyline, desipramine (antidepressants)
  - Opiates
  - tramadol
- Consider safety and tolerability when initiating treatment

### Mechanisms of Action: Analgesic Agents

- **Anticonvulsants**
  - sodium-channel blockade; calcium-channel blockade
- **Tricyclic Antidepressants**
  - inhibit reuptake of norepinephrine and serotonin into presynaptic neurons
- **Opioids**
  - block neurotransmitter-release by nociceptive fibers, thus decreasing transmission of pain-producing signals
- **Topicals**
  - sodium-channel blockade; vanilloid receptor (VR1)

### FDA-Approved Treatments for Neuropathic Pain

- **Lidocaine Patch 5%** - post herpetic neuralgia
- **Gabapentin** - post herpetic neuralgia
- **Carbamazepine-trigeminal neuralgia**
- **Duloxetine** - diabetic peripheral neuropathic pain
- **Pregabalin** - neuropathic pain associated with Diabetes/PHN
- **Ziconotide**

### Topical Treatments for Neuropathic Pain

- **Aspirin preparations**
  - eg, aspirin in chloroform or ethyl ether
- **Capsaicin**
  - extracted from chili peppers
- **EMLA** (eutectic mixture of local anesthetics)
- **Topical lidocaine patch 5%**

### Topical vs Transdermal Drug Delivery Systems

<table>
<thead>
<tr>
<th>Topical (lidocaine patch 5%)</th>
<th>Transdermal (fentanyl patch)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral tissue activity</td>
<td>Systemic activity</td>
</tr>
<tr>
<td>Applied directly over painful site</td>
<td>Applied away from painful site</td>
</tr>
<tr>
<td>Insignificant serum levels</td>
<td>Serum levels necessary</td>
</tr>
<tr>
<td>Systemic side effects unlikely</td>
<td>Systemic side effects</td>
</tr>
</tbody>
</table>

### Lidocaine Patch 5% Therapy for PHN

Anticonvulsants

- Carbamazepine*
- Divalproex sodium*
- Gabapentin*
- Lamotrigine
- Topiramate*
- Zonisamide
- Oxcarbazepine
- Levatriacetam
- Pregabalin
- Clonazepam
- Phenoytin
- Tiagabine

*Has FDA indication for pain/headache

<table>
<thead>
<tr>
<th>Anticonvulsant Drugs for Neuropathic Pain Disorders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Postherpetic neuralgia</td>
</tr>
<tr>
<td>- gabapentin</td>
</tr>
<tr>
<td>- pregabalin</td>
</tr>
<tr>
<td>• Diabetic neuropathy</td>
</tr>
<tr>
<td>- carbamazepine</td>
</tr>
<tr>
<td>- phenytoin</td>
</tr>
<tr>
<td>- gabapentin</td>
</tr>
<tr>
<td>- Lamotrigine</td>
</tr>
<tr>
<td>- pregabalin</td>
</tr>
<tr>
<td>• HIV-associated neuropathy</td>
</tr>
<tr>
<td>- lamotrigine</td>
</tr>
<tr>
<td>• Trigeminal neuralgia</td>
</tr>
<tr>
<td>- carbamazepine</td>
</tr>
<tr>
<td>- lamotrigine</td>
</tr>
<tr>
<td>- oxcarbazepine</td>
</tr>
<tr>
<td>• Central poststroke pain</td>
</tr>
<tr>
<td>- lamotrigine</td>
</tr>
</tbody>
</table>

Gabapentin in Neuropathic Pain Disorders

- FDA approved for postherpetic neuralgia
- Anticonvulsant: uncertain mechanism
- Limited intestinal absorption
- Usually well tolerated; serious adverse effects rare
  - dizziness and sedation can occur
- No significant drug interactions
- Peak time: 2 to 3 h; elimination half-life: 5 to 7 h
- Usual dosage range for neuropathic pain up to 3,600 mg/d (tid–qid)*

*Not approved by FDA for this use.

Gabapentin in the Treatment of Postherpetic Neuralgia

<table>
<thead>
<tr>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=116)</td>
</tr>
<tr>
<td>Gabapentin (n=109)</td>
</tr>
<tr>
<td>Moderately or much improved</td>
</tr>
<tr>
<td>Minimally improved</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>Worse</td>
</tr>
</tbody>
</table>


Gabapentin in the Treatment of Painful Diabetic Neuropathy*

<table>
<thead>
<tr>
<th>Mean pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>N=165</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

*Not approved by FDA for this use.

Antidepressants in Neuropathic Pain Disorders*

- Multiple mechanisms of action
- Randomized controlled trials and meta-analyses demonstrate benefit of tricyclic antidepressants (especially amitriptyline, nortriptyline, desipramine) for postherpetic neuralgia and diabetic neuropathy
- Selective serotonin reuptake inhibitors (SSRIs): inconsistent in diabetic neuropathy
- Onset of analgesic variable
  - analgesic effects independent of antidepressant activity
- Improvements in insomnia, anxiety, depression
- Desipramine and nortriptyline have fewer adverse effects

*Not approved by FDA for this use.
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Tricyclic Antidepressants: Adverse Effects

- Commonly reported AEs (generally anticholinergic):
  - blurred vision
  - cognitive changes
  - constipation
  - dry mouth
  - orthostatic hypotension
  - sedation
  - sexual dysfunction
  - tachycardia
  - urinary retention

AEs = adverse effects.

Fewest AEs

• Desipramine
• Nortriptyline
• Imipramine
• Doxepin

Most AEs

• Amitriptyline

Nortriptyline vs Amitriptyline

- No differences seen in efficacy
  - relief of steady, brief, or skin pain
  - mood, disability, or satisfaction
  - patient preference for either drug
- Randomized, double-blind crossover trial of safety and efficacy of nortriptyline vs amitriptyline in postherpetic neuralgia*
- Intolerable side effects more frequent with amitriptyline
- Use drug with fewer side effects

*Not approved by FDA for this use.

Tricyclic Antidepressants for Neuropathic Pain Disorders

- Can split dose to reduce side effects
- Expect partial effect
  - use multiple agents (other classes)
- Consider preprescription cardiac evaluation
- Not being used simultaneously to treat depression
- Start at 10 to 25 mg at bedtime
  - increase every week as tolerated to a target dose of 25 to 150 mg
  - expect individual variability in treatment response

Principles of Opioid Therapy for Neuropathic Pain

- Opioids should be titrated for therapeutic efficacy versus side effects
- Fixed-dose regimens are generally preferred over prn regimens
- Document treatment plan and outcomes
- Consider use of an opioid written care agreement
- Opioids can be effective in neuropathic pain
- Most opioid side effects can be controlled with appropriate specific management (eg, prophylactic bowel regimen, use of stimulants)
- Understand distinction between addiction, tolerance, physical dependence, and pseudoaddiction

Distinguishing Dependence, Tolerance, and Addiction

- Physical dependence: a withdrawal syndrome would arise if a drug is discontinued, dose is substantially reduced, or antagonist is administered
- Tolerance: a greater amount of drug is needed to maintain therapeutic effect, or loss of effect over time
- Pseudoaddiction: behavior suggestive of addiction; caused by under-treatment of pain
- Addiction (psychological dependence): a psychiatric disorder characterized by continued compulsive use of a substance despite harm

Opioid Efficacy Studies in Neuropathic Pain Disorders

- Nonmalignant neuropathic pain disorders
  - IV fentanyl
  - levorphanol
- Postherpetic neuralgia
  - IV morphine
  - controlled-release oxycodone
  - Morphine/methadone
- Phantom limb pain
  - oral morphine
- Diabetic neuropathy
  - tramadol
  - oxycodone
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Efficacy of Controlled-Release Oxycodone in Postherpetic Neuralgia

![Graph showing VAS pain intensity](image)

- Placebo
- CR oxycodone

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Placebo</th>
<th>CR oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady pain</td>
<td>55</td>
<td>34</td>
</tr>
<tr>
<td>Brief pain</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Allodynia</td>
<td>32</td>
<td>22</td>
</tr>
</tbody>
</table>

*Not approved by FDA for this use.


Efficacy of Tramadol in Painful Polyneuropathy

![Graph showing median rating](image)

- Placebo
- Tramadol

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Median rating (0-10 point scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>6</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
</tr>
<tr>
<td>Touch-evoked pain</td>
<td>5</td>
</tr>
</tbody>
</table>


Oral Opioid Therapy With Levorphanol Reduces Chronic Neuropathic Pain

- Levorphanol: μ-opioid agonist
- 81 patients in randomized double-blind study who failed previous therapy (antidepressants, NSAIDs, anticonvulsants) for neuropathic pain
  - two groups randomized to 0.75-mg or 0.15-mg capsules
- 36% greater reduction of pain in high-dose compared with 21% in low-dose group (P<.02)
  - of all patients given 0.75 mg, 47% reported moderate or better pain relief
  - of patients receiving 0.75 mg who completed study, 48% claimed less pain and 66% had moderate or better pain relief
- 12 patients in high-dose and 3 patients in low-dose groups withdrew because of adverse events


Interventional Treatments for Chronic Pain

- 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

CRPS = complex regional pain syndrome.

Summary

- Chronic pain is a disease, not a symptom
- “Rational” multi-drug therapy is often necessary
  - combining peripheral and central nervous system agents enhances pain relief
- Treatment goals include:
  - balancing efficacy, safety, and tolerability
  - reducing baseline pain and pain exacerbations
  - improving function and QOL
- New agents and new uses for existing agents offer additional treatment options