Neuropathic Pain Associated with Common Medical Conditions

26th Annual Medical Surgical Nursing Conference

Christine Miaskowski, RN, PhD, FAAN
American Cancer Society Clinical Research Professor
and
Sharon Lamb Endowed Chair in Symptom Management Research
Department of Physiological Nursing
University of California, San Francisco
Objectives

• Define neuropathic pain
• Describe the mechanisms that underlie neuropathic pain and its associated clinical symptoms
• Describe the assessment of neuropathic pain
• Provide evidenced-based recommendations for the pharmacologic management of neuropathic pain
• Provide evidenced-based recommendations for the non-pharmacologic management of neuropathic pain
Types of Pain and Definitions

• Nociceptive pain (e.g., arthritis)
  • Involves peripheral sources of noxious stimulation
    • Inflammatory mediators
  • Otherwise the nervous system is normal

• Neuropathic pain (*IASP definition, 2011*)
  • Pain caused by a lesion or disease of the somatosensory system
  • Lesion leads to an abnormal or dysfunctional somatosensory system
  • Refers to a broad range of clinical conditions
    • Anatomic categorization (e.g., peripheral vs central)
    • Etiological categorization (e.g., degenerative, traumatic, infectious, metabolic, toxic)
# Classification of Neuropathic Pain

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Peripheral</th>
<th>Spinal</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Fabray disease</td>
<td>Syringomyelia</td>
<td>Syringobulbia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Diabetes</td>
<td>$B_{12}$ myelopathy</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Nerve injury</td>
<td>SCI</td>
<td>MS</td>
</tr>
<tr>
<td>Vascular</td>
<td>Vasculitic</td>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Tumor compression</td>
<td>Tumor compression</td>
<td>Tumor compression</td>
</tr>
<tr>
<td>Infectious</td>
<td>HIV, PHN</td>
<td>Infectious myelitis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Toxic</td>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology of Neuropathic Pain

• Difficult to describe the epidemiology of neuropathic pain
  • Diverse number of medical conditions

• ~7% to 8% of the general population
• ~25% of patients with diabetes
• ~35% of patients with HIV disease
• ~20% of patients with cancer
• ~25% of patients with herpes zoster infection develop post herpetic neuralgia
Assessment of Neuropathic Pain

• Detailed history
  • Onset
  • Description
  • Location
  • Severity
  • Aggravating and relieving factors
  • Previous treatments and their effectiveness
  • Associated symptoms
• Physical examination
  • Sensory examination
  • Motor examination
  • Balance
Clinical Characteristics of Neuropathic Pain

- Consist of both positive and negative phenomena
- Positive phenomena
  - Spontaneous pain
  - Allodynia – pain triggered by normally non-noxious stimuli
  - Hyperalgesia – exaggerated response to normally non-noxious stimuli
  - Non-painful sensations
    - Paresthesias
    - Dysesthesias
- Negative phenomena
  - Sensory deficits
  - Motor deficits
Peripheral Neuropathy:
Diabetic neuropathy

Entrapment Neuropathy:
Lateral femoral cutaneous nerve,
Median nerve

Lumbar radiculopathy:
Left L4

Postherpetic neuralgia:
Left T4
Aggravating and Relieving Factors

• Patients can experience evoked pain
• Pain can occur with activity
• Mechanical allodynia – pain as a result of mechanical or thermal stimuli
  • Clothes rubbing against a site
  • Cold allodynia or hyperalgesia is more common than heat
Associated Symptoms

- Depression
- Anxiety
- Fatigue
- Sleep disturbance
- Significant impairments in functional status
- Significant impairments in employment status
- Significant decrements in QOL
Sensory Examination

• Light touch sensation
  • Protective sensation
  • Sharp or dull
  • Monofilament testing
• Temperature sensation
  • Hot
  • Cold
• Vibration
  • Tuning fork
Sensory Examination

• Light touch sensation
  • Protective sensation
  • Sharp or dull
  • Monofilament testing

• Temperature sensation
  • Hot
  • Cold

• Vibration
  • Tuning fork
Sensory Examination

• Light touch sensation
  • Protective sensation
  • Sharp or dull
  • Monofilament testing
• Temperature sensation
  • Hot
  • Cold
• Vibration
  • Tuning fork
Motor Examination

• Deep tendon reflexes

• Balance
  • Fullerton Advanced Balance Scale test – research tool
  • Timed Get Up and Go Test (TUG) – clinically useful measure
    • Normal value = 12 seconds
STEP 1
Sit to stand

STEP 2
Walk 3 meters

STEP 3
Turn around

STEP 4
Walk 3 meters

STEP 5
Sit down
SIT-STAND

OBSERVE
- difficulty/falling back
- swaying

WALK 3 m
- posture,
- stride length and symmetry
- foot clearance + heel strike
- arm swing
- shuffling/spastic
- hemiparetic
- antalgic

PROBLEMS
- fear of falling
- Parkinson’s, myelopathy
- CVA, arthritis

Poor postural control

180° TURN
> 3 steps
- staggering
Pharmacologic Management

• Evidenced-based guidelines published by the IASP Special Interest Group on Neuropathic Pain
  • Systematic review and meta-analysis of the literature
• Most of the literature is in diabetic neuropathy and post herpetic neuralgia
• 30% rule
Perception
Cognitive behavioral approaches

Descending inhibition
TCAs: e.g. nortriptyline
SNRIs: e.g. duloxetine
Opioids: e.g. morphine

Spinal transmission
GABAr: e.g. gabapentin
NMDAr: e.g. ketamine
Opioids: e.g. morphine

Peripheral transduction
VGSC: e.g. lidocaine, carbamazepine
TRPV1: e.g. capsaicin
TCAs: e.g. nortriptyline

Cerebral cortex
Thalamus
PAG
RVM
Spinal cord
dorsal horn
DRG
Strong Recommendations – First Line Management

- Gabapentin (Neurontin)
- Gabapentin extended release (Gralise)
- Pregabalin (Lyrica)
- Serotonin-noradrenaline reuptake inhibitors
  - Duloxetine (Cymbalta)
  - Venlafaxine (Effexor)
- Tricyclic antidepressants
Gabapentin (Neurontin)

- Beginning dose = 100 to 300 mg every night or 100 to 300 mg TID
- Titration – increase by 100 to 300 mg three times daily every 1 to 7 days as tolerated
- Maximum dose = 1200 mg TID
- Adequate trial = 3 to 8 weeks for titration plus 2 weeks at maximum tolerated dose
- Side effects – sedation, dizziness, weight gain, edema, blurred vision
- Simple antacids reduce bioavailability
- Follow-up on weight gain (e.g., diabetics)
Pregabalin (Lyrica)

• Beginning dose = 50 mg TID or 75 mg BID
• Titration – increase by 300 mg daily after 3 – 7 days, then by 150 mg/d every 3 to 7 days as tolerated
• Maximum dose = 300 to 600 mg in two divided doses
• Adequate trial = 4 weeks
• Side effects – sedation, dizziness, weight gain, edema, blurred vision
• Onset of pain relief may be more rapid
Duloxetine (Cymbalta)

- Serotonin-noradrenaline reuptake inhibitor
- Most studies and therefore recommended first
- Maximum dose = 300 to 600 mg in two divided doses
- Side effects – nausea, loss of appetite, constipation, sedation, dry mouth, anxiety
- Use with caution in patients with a history of mania, seizures, bleeding tendency, taking anticoagulants, concomitant SSRI or tramadol treatment
- Contraindicated in patients on MAO inhibitors; uncontrolled hypertension
- Blood pressure monitoring is needed
Venlafaxine (Effexor - ER)

• Serotonin-noradrenaline reuptake inhibitor
• Maximum dose = 150-225 mg once a day in the extended release formulation
• Side effects – nausea, loss of appetite, hypertension, sedation, insomnia, constipation, dry mouth, anxiety
• Use with caution in patients with hypertension, concomitant SSRI or tramadol treatment
• Contraindicated in patients on MAO inhibitors
• Blood pressure monitoring is needed
Antidepressants

- 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 analgesia variable
  - analgesic effects independent of antidepressant activity
  - Improvements in insomnia, anxiety, depression
Antidepressants

• Beginning dose = 10 to 25 mg at night
• Titration – increase dose by 10 to 25 mg/day, every 3 to 7 days as tolerated
• Maximum dose = 25 to 150 mg/day
• Tertiary amine TCAs (amitriptyline, imipramine) are not recommended at doses of >75 mg/day in adults ≥ 65 years of age
• Increased risk of sudden cardiac death was reported with TCA doses of >100 mg/day
Tricyclic Antidepressants: Adverse Effects

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

Fewest AEs

• Desipramine
• Nortriptyline
• Imipramine
• Doxepin
• Amitriptyline

Most AEs
Antidepressants

• Use with caution in patients with:
  • History of seizures
  • Prostatic hypertrophy
  • Urinary retention
  • Chronic constipation
  • Narrow angle glaucoma
  • Increased intraocular pressure
  • Suicidal ideation
  • Concomitant use of SSRI, SNRI, or tramadol

• Contraindicated in patients recovering from MI or with heart block and patients on MAO inhibitors

• ECG screening is recommended in adults >40

• ECG and blood concentration follow needed at doses of > 150 mg/day
Weak Recommendations – Second or Third Line Management

- Capsaicin 8% patches - second
- Lidocaine patches - second
- Tramadol - second
- Botulinum toxin A (SQ injection) – third
- Strong opioids - third
Topical Lidocaine Patch

• Lidocaine 5% in pliable patch
• Up to 3 patches applied once daily directly over painful site
  • 12 h on, 12 h off (FDA-approved label)
  • Published data indicate 4 patches (18–24 h) safe
  • Adequate trial is 2 weeks
• Efficacy demonstrated in 3 randomized controlled trials on post herpetic neuralgia
• Systemic side effects unlikely
  • most common side effect: application-site sensitivity
• Clinically insignificant serum lidocaine levels
• Mechanical barrier decreases allodynia
Capsaicin 8% Patch

• High concentration of synthetic capsaicin
• Selective agonist of TRPV1 – temporary dysfunction of peripheral nociceptors
• Approved for PHN in US
• 30-60 minute application of one to four patches every three months
• Transient application site reactions (redness, transient increase in pain)
Capsaicin Patch
Neuropathy Treatment Procedure
Tramadol Hydrochloride

• Mechanism of action
  • Norepinephrine and serotonin reuptake inhibitor
  • Opioid agonist
• Beginning dose = 50 mg 1x or 2x/day
• Titration = increase by 50 to 100 mg/day in divided doses every 3 to 7 days as tolerated
• Maximum dose = 400 mg/day; in patients over 75 give 300 mg/day in divided doses
• Adequate trial = 4 weeks
Inconclusive Recommendations

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lacosamide
- Lamotrigine
- NMDA antagonists
- Oxcarbazepine
- SSRI antidepressants
- Tapentadol
- Topiramate
- Zonisamide
Weak Recommendations
Against Use

- Cannabinoids
- Valproate
Strong Recommendations Against Use

- Levetiracetam (Keppra)
- Mexiletine
Non-pharmacologic Treatments

• Cognitive behavioral therapy
• Physical therapy
• Nerve blocks
• Integrative medicine
  • Acupuncture
  • Massage
  • Relaxation
  • Meditation
Overall Management of Neuropathic Pain

• No single treatment is completely effective
  • Decrease pain
  • Improve function
• Need to address the psychological component of chronic pain
• Patients may need a multidisciplinary pain clinic