Front Line Pain Management: Evidence-based non-opioid pharmacotherapy for the treatment of common neuropathic pain syndromes

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Disclosures

No financial disclosures or conflicts of interest

Off-label use of medication will be discussed
Learning Objectives

1. Describe the pathophysiology of pain as it pertains to neuropathic versus nociceptive pain
2. Employ evidence-based pain assessment techniques to identify neuropathic pain
3. Recall adjuvant and coanalgesic pharmacotherapy utilized for the treatment of neuropathic pain
4. Devise evidence-based recommendations for non-opioid pharmacotherapy to treat common neuropathic pain syndromes
Purpose

- 2012 NIH survey reports 11.2% of U.S. adults experience daily pain
- More than 11.5 million Americans (12 years of age or older) reported misusing prescription opioids in 2016
- 1999-2014: 165,000 people in the U.S. died from prescription opioids
- Up to 10% of the global population may be suffering from chronic neuropathic pain
WHO Analgesic Ladder

**Step 1:**
Nonopioid analgesic ± Adjuvant

**Step 2:**
Opioid for mild-moderate pain ± Nonopioid analgesic ± Adjuvant analgesic

**Step 3:**
Opioid for moderate-severe pain ± Nonopioid analgesic ± Adjuvant analgesic

Increasing pain
Describe the pathophysiology of pain as it pertains to neuropathic versus nociceptive pain
Pathophysiology of Pain

- Body is equipped with different types of sensory neurons
  - Mechanoreceptors
  - Thermoreceptors
  - Chemoreceptors
  - Nociceptors

- Nociceptors: Sensory neurons that function primarily to perceive pain
- Nociception: Encoding of noxious stimuli that can cause tissue damage
Pathophysiology of Neuropathic Pain

- Lesions or disease of somatosensory pathways lead to loss of function and paradoxically increased pain sensitivity and spontaneous pain.
- Highly variable etiology:
  - Infection
  - Toxins
  - Spinal cord compression/entrapment
- Serves no protective function.
- Primarily chronic in nature.
Classification of Neuropathic Pain

- Central neuropathic pain involves neuropathic pain associated with the spinal cord or brain

Examples include:
  - Spinal Cord injury
  - Post-stroke neuropathy
  - Multiple sclerosis neuropathic pain
  - CNS malignancy
Classification of Neuropathic Pain

- **Peripheral neuropathic pain** involves neuropathic pain associated with damage to the peripheral somatosensory system.

- Examples include:
  - Chemotherapy-induced PN
  - Diabetic PN
  - Trigeminal neuralgia
  - Postherpetic neuralgia
Case Study #1

KB is a 46 year old male who presents to your community pharmacy with a sullen look on his face. He confided in you several months ago that he was diagnosed with stage 4 lung cancer. He’s been undergoing chemotherapy and has been receiving high doses of morphine and fentanyl to manage his pain, yet his pain still seems to be unmanaged as evidenced by early refill requests for his short acting opioid, reports from close family members, and the non-verbal indicators of pain that you notice when you’re counseling him on his new prescription for duloxetine. You then ask him about his pain and he describes it as intermittent stabbing, shooting pain that runs down the length of his right leg. He also states that he feels a dull, achy pain on the right side of his abdomen. He rates his pain a 9/10 on average, with 7/10 being the lowest and 10/10 being the highest.
Question #1:

Which of the following neuropathic pain pathologies is plausible for KB?

a. Toxic (chemotherapy-induced)
b. Trigeminal neuralgia
c. Neoplastic
d. Degenerative
e. A and C
f. B and C
g. None of the above
Employ evidence-based pain assessment techniques to identify neuropathic pain
Principles of Pain Assessment for Pharmacists

- Identify characteristics of pain
- Determine potential mechanism(s) of pain
- Clarify precipitating and palliating factors
- Understand patient-centric goals of care
- Referral, monitoring, and follow-up
Principles of Pain Assessment for Pharmacists

- Patient interview
  - Medical history
  - Onset
  - Location(s)
  - Intensity
  - Severity
  - Level of disability
  - Impact on sleep and quality of life

- PQRSTU method
## Pain Assessment - Differentiation of Pain Types

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Quality Description</th>
<th>Features</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive-Somatic</td>
<td>Throbbing, aching, stabbing, squeezing, dull</td>
<td>Easily located</td>
<td>Bone Metastases</td>
</tr>
<tr>
<td>(musculoskeletal)</td>
<td></td>
<td>Inflammation very common</td>
<td>Wounds</td>
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<tr>
<td></td>
<td></td>
<td>Worsened by movement</td>
<td>Joint pain</td>
</tr>
<tr>
<td>Nociceptive-Visceral</td>
<td>Sharp, throbbing, cramping, gnawing, aching</td>
<td>Hard to locate</td>
<td>Angina</td>
</tr>
<tr>
<td>(organ and deep tissue)</td>
<td></td>
<td>Inflammation common</td>
<td>Irritable bowel syndrome</td>
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<td></td>
<td></td>
<td></td>
<td>Referred pain</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Electrocuting, “pins and needles”, burning, shooting, itchy, tingling, numbness</td>
<td>Radiation along areas of nerve innervation</td>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>(CNS and PNS)</td>
<td></td>
<td>“Travels down” or “.. across”</td>
<td>Diabetic neuropathy</td>
</tr>
</tbody>
</table>
Pain Assessment - Severity

- “On a scale of 0 to 10, how would you rate your pain today?”
- Gold standard for pain assessment in verbal cancer patients
- Three commonly-used modalities:
  - Visual analogue scale (VAS)
    - 0-100 mm
  - Numeric rating scale
    - Pain on a scale of 0-10
  - Categorical scale
    - Mild, moderate, or severe
- Pay attention to time frame
Neuropathic Pain Assessment for Pharmacists

- Patient interview may suggest nociceptive, neuropathic, or mixed pain modality
- Validated screening tools available if needed
  - Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)
  - Douleur neuropathique en 4 questions (DN-4)
  - Neuropathic Pain Questionnaire (NPQ)
- Patient interview alone may suffice
Neuropathic Pain Questionnaire

1. Burning Pain
   Rating:___________ x 0.006 =
2. Overly Sensitive to Touch
   Rating:___________ x 0.005 =
3. Shooting Pain
   Rating:___________ x 0.005 =
4. Numbness
   Rating:___________ x 0.020 =
5. Electric Pain
   Rating:___________ x -0.008 =
6. Tingling Pain
   Rating:___________ x 0.010 =
7. Squeezing Pain
   Rating:___________ x -0.004 =
8. Freezing Pain
   Rating:___________ x 0.004 =
9. How unpleasant is your usual pain?
   Rating:___________ x 0.006 =
10. How overwhelming is your usual pain?
    Rating:___________ x -0.003 =
11. Increased pain to touch
    Rating:___________ x 0.006 =
12. Increased pain due to weather changes
    Rating:___________ x -0.005 =

Total Discriminant Function Score:
Below 0 = Predicts non-neuropathic pain
At or above 0 = Predicts neuropathic pain

NeuPSIG Neuropathic Pain Algorithm

Possible neuropathic pain as evidenced by pain along the pathway of nerve innervation

Confirmatory Tests
  a. Presence of positive or negative sensory symptoms
     a. Diagnostic test
        i. ENPG
        ii. MRI

Neither

Unconfirmed

Both

Definite neuropathic pain

One

Likely neuropathic pain
Case Study #2

Patient SC is an 83 year old female patient residing in a long-term care facility. Her past medical history includes CAD, CHF, CVD, HTN, COPD, DM2, and CKD 4. She is cognitively intact. You are reviewing her medication list and notice that the attending physician initiated gabapentin 3 days ago. Documentation of the indication for the gabapentin is missing from the patient’s chart. The current dose of gabapentin is 300 mg PO BID. Concurrent opioid and non-opioid analgesic therapy includes oxycodone 5 mg tablet PO q4h prn pain and acetaminophen 500 mg tablet PO q4h prn pain.
Question #2 and 3

What questions do you have for AB to elucidate the potential indication for gabapentin therapy?

True or False:
This patient may be experiencing both nociceptive and neuropathic pain
Recall adjuvant and coanalgesic pharmacotherapy utilized for the treatment of neuropathic pain.
Gabapentin and Gabapentin Enacarbil

- Combined NNT = 7.2 (reduce pain score by 30-50%)
- First line
- Effective Dose: 1200-3600 mg/day
- Saturable absorption (nonlinear PK)
- Renal dosing (eliminated as 100% unchanged drug via the urine)
- Opioid sparing

Lancet Neurol. 2015 Feb;14(2):162-73
Cochrane Database Syst Rev. 2017 Jun 9;6:CD007938
Pregabalin

- Combined NNT = 7.7 (reduce pain score by 30-50%)
- First line
- Effective dose: 150-600 mg/day
- Improved analgesia with escalating doses
- Renal dosing required (eliminated as 90% unchanged drug via urine)
- Opioid sparing

Lancet Neurol. 2015 Feb;14(2):162-73
SNRI’s (duloxetine and venlafaxine)

- Combined NNT = 6.4 (reduce pain score by 30-50%)
- First line

**Venlafaxine**
- Effective dose: 150 mg/day or higher
- SSRI in low doses (37.5 mg/day), SNRI at higher doses (≥ 225 mg/day)

**Duloxetine**
- Effective dose: 60-120 mg/day
Tricyclic Antidepressants

- Combined NNT = 3.6 (reduce pain score by 30-50%)
- First line
- Preferable to utilize secondary amines versus tertiary amines
  - Similar efficacy between agents
  - Tertiary amines - Higher degree of sedation, anticholinergic side effects
  - Adverse effects pronounced in elderly
- 75 mg/day max dose of tertiary amines in patients ≥ 65 years old
Second and Third Line Adjuvant Analgesics

- Capsaicin 8% patches (not available OTC)
  - Combined NNT = 10.6 (reduce pain score by 30-50%)
  - Dose: 1-4 patches to painful area(s) for 30-60 mins q3months
  - Peripheral neuropathic pain only

- Lidocaine patches
  - Dose: 1-3 patches to painful area(s) once a day q12h on and q12h off
  - Peripheral neuropathic pain only

- Botulinum toxin A
  - Administered subcutaneously
  - 50-200 units to painful area(s) q3months
  - Peripheral neuropathic pain only

Lancet Neurol. 2015 Feb;14(2):162-73
Second and Third Line Adjuvant Analgesics

- Cannabis
- Capsaicin cream
- SSRI’s
- Topiramate
- Zonisamide
Case Study #3

Patient JT is a 32 year old female who recently moved into the area and is presenting to your primary care clinic. Prior to initial review of her medications and supplements, she states that she suffered from a shingles outbreak in August of 2018. She is experiencing pain along the path of the resolved shingles rash, which confuses her and is interfering with her emotional and social well-being.

PMH is unremarkable.
Question #3

Which of the following adjuvant analgesics would likely be ineffective for treating this patient’s neuropathic pain? (Choose all that apply)

A. Carbamazepine
B. Gabapentin
C. Duloxetine
D. Topical lidocaine patch
E. Escitalopram
F. Capsaicin cream
G. Imipramine
Devise evidence-based recommendations for non-opioid pharmacotherapy to treat common neuropathic pain syndromes
Diabetic Peripheral Neuropathy (DPN)

- 9.4% of US population diagnosed with diabetes
- Approximately 30-50% of these patients develop DPN
- Symptoms include:
  - Pain
  - Numbness
  - Paresthesia
- First step in managing DPN is glycemic control
Diabetic Peripheral Neuropathy (DPN)

- 2017 systematic review concluded the following agents were likely effective for DPN (strength of evidence)
  - Pregabalin (Low)
  - Oxcarbazepine (Low)
  - Duloxetine (Moderate)
  - Venlafaxine (Moderate)
  - TCA’s (Low)
  - Botulinum toxin (Low)

- JAMA 2018 Clinical Evidence Synopsis adds gabapentin to this list

- Scarcity of head-to-head trials to compare efficacy

JAMA. 2018;319(8):818-819
Postherpetic Neuralgia (PHN)

- Three phases of pain associated with herpes zoster infection:
  - **Acute** - Preceding or accompanying eruption of rash and persists up to 30 days from onset
  - **Subacute** - Pain that persists beyond healing of rash but resolves within 4 months
  - **Postherpetic neuralgia** - Pain persisting beyond 90 days from initial onset of rash

- Debilitating pain that can significantly impact QOL, especially in older adults

- Pain management strategies should focus on symptom management

- Some patients have symptom resolution after several years
Postherpetic Neuralgia (PHN) - Topical Therapy

- Lidocaine patches
  - 5% patch indicated for PHN
    - Limited evidence of benefit
    - Expensive
  - 4% OTC patch indicated for minor pain
    - Inexpensive

- Capsaicin
  - 8% patch (not available OTC, $$$$)
    - NNT = 7 (50% reduction in pain)
    - Painful application, pretreat

Am Fam Physician. 2017 Nov;96(10):656-663
Postherpetic Neuralgia (PHN) - Oral Therapy

- Gabapentin
  - NNT = 8 (50% reduction in pain)
  - 1800–3600 mg/day

- Pregabalin
  - NNT = 4 (50% reduction in pain)
  - 600 mg/day

- TCA’s (amitriptyline, nortriptyline, desipramine)
  - NNT = 3 (50% reduction in pain)
  - No significant differences between agents in terms of efficacy
Toxic Neuropathies

- Neuropathies caused by industrial toxins, heavy metals, drugs, or alcohol
- Reversal of symptoms typically occurs after stopping offending agent(s)
- Accurate medication history essential (including OTC supplements [i.e. B6])
- Major dose-limiting side effect of commonly-used chemotherapy
### Pharmacotherapy Associated with Peripheral Neuropathies

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Cardiovascular</th>
<th>Antimicrobials</th>
<th>CNS Agents</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum compounds</td>
<td>Amiodarone</td>
<td>Dapsone</td>
<td>Nitrous oxide</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Isoniazid</td>
<td>Phenelzine</td>
<td>Phenytoin</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Linezolid</td>
<td>Metronidazole</td>
<td></td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>NRTI’s</td>
<td></td>
<td></td>
<td>Leflunomide</td>
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<tr>
<td>Vinca alkaloids</td>
<td>Fluoroquinolones</td>
<td></td>
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<td>Sulfasalazine</td>
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<td>5-FU</td>
<td>Azoles</td>
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<td>Cytarabine</td>
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<td>Gemcitabine</td>
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<td>Ifosfamide</td>
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Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- Lack of high-quality evidence to guide treatment
- No recommended agents to prevent CIPN
- Duloxetine (moderate SOE) is only agent recommended for CIPN
- Evidence is inconclusive for other therapies
Cancer-related Neuropathic Pain

- Etiology of cancer pain is typically mixed mechanism
  - Rarely presents as purely nociceptive or neuropathic
  - Often presents at multiple sites with multiple etiologies
    - Inflammatory
    - Neuropathic
    - Ischemic

- Severity of neuropathic cancer pain follows disease progression
- Estimated 40% prevalence of neuropathic pain in patients with cancer
Cancer-related Neuropathic Pain

- Antidepressants and anticonvulsants recommended first line
- Drug selection may be based off of other symptoms and comorbidities
  - SNRI for concomitant anxiety/depression
  - TCA for concomitant insomnia
- Trial and error may occur when finding an effective agent for an individual
- Corticosteroids included as an adjuvant for these patients
  - Usually dexamethasone
  - Useful for acute management of a pain crises

Refractory Cancer-related Neuropathic Pain

- Lidocaine may be administered intravenously for refractory cancer pain
- Small studies/case reports support its use for opioid-refractory cancer pain
- May be able to reduce analgesic requirements
- Adverse effects include tinnitus, lightheadedness, sedation, and headache
- Dosing:
  - Bolus: 1-3 mg/kg given over 20-30 mins
  - Continuously infuse at 0.5-2 mg/kg/hr (100 mg/hr max)

Clin J Pain. 2006 Mar-Apr;22(3):266-71
J Pain Symptom Manage. 2009 Jan;37(1):85-93
Neuropathic Pain in Multiple Sclerosis

- Most common inflammatory demyelinating disease of CNS
- MS-related pain prevalence ranges from 40-86% of patients
  - Often multifactorial
  - Peripheral neuropathies occur in approximately 25% of patients
  - Trigeminal neuralgia occurs in approximately 4% of patients
- First line pharmacotherapy
  - TCA’s, SNRI’s, gabapentin, pregabalin (central neuropathic pain)
  - Carbamazepine/oxcarbazepine (trigeminal neuralgia or L’hermitte’s signs)
Neuropathic Pain in Amyotrophic Lateral Sclerosis

- Rare neurodegenerative disease with a fatal outcome 2-4 years from onset
- Pain reported by most patients with ALS
  - Unable to currently support hypothesis that most pain in most patients is neuropathic
  - Pain is largely multifactorial
- First line pharmacotherapy
  - Gabapentin: 900-3600 mg/day
  - Pregabalin: 150-600 mg/day
  - TCA’s

Lancet Neurol. 2017;16(2):144
Case Study #4

(Patient from Case Study #1) KB’s wife AB walks into your community pharmacy two months after his last visit to the pharmacy. You discuss KB’s current situation with his wife and she confides that he is being admitted into hospice services today. Duloxetine had been titrated up to a dose of 90 mg PO once daily without reduction in his pain intensity. Additionally, escalating doses of morphine have not correlated with an increase in pain control. In fact, AB states that “the pain just seems to get worse with escalating doses”. His pain is currently an 8/10, with the lowest being a 6/10 and highest at a 10/10.
Question # 4

What positive sensory feature of neuropathic pain is KB experiencing?
Question # 5

Please design a pharmacotherapy care plan aimed at treating this patient’s neuropathic pain. This care plan should include:

Problem + Current Therapy + Recommendation(s) + Monitoring/Follow Up
Questions/Comments?


