The Agony of de Feet: Treatment Strategies for Diabetic Peripheral Neuropathy

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Peripheral Neuropathy

= Disorder or series of disorders affecting the peripheral nervous system
**Diabetic Peripheral Neuropathy (DPN)**

- Most common complication of diabetes
  - ~50% of all patients with diabetes
  - Most common cause of foot ulceration
  - Primary factor for non-traumatic amputations
- Annual cost = ~$11 billion

www.diabetes.org

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**Loss of Sensation Can Lead to Injury!**
## Typical Descriptors for Neuropathic Pain

<table>
<thead>
<tr>
<th>Painful</th>
<th>Non-painful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>Asleep</td>
</tr>
<tr>
<td>Knife-like</td>
<td>“Dead”</td>
</tr>
<tr>
<td>Electrical</td>
<td>Numbness</td>
</tr>
<tr>
<td>Squeezing</td>
<td>Tingling</td>
</tr>
<tr>
<td>Constricting</td>
<td>Prickling</td>
</tr>
<tr>
<td>Throbbing</td>
<td></td>
</tr>
<tr>
<td>Freezing</td>
<td></td>
</tr>
<tr>
<td>Hurting</td>
<td></td>
</tr>
<tr>
<td>Allodynia</td>
<td></td>
</tr>
</tbody>
</table>
Management of DPN

1. Rule out other peripheral neuropathies and non-neurological painful and disabling conditions prior to diagnosis/treatment of DPN
2. Long-term control of blood glucose is the cornerstone of treatment/prevention
3. Screening for DPN is essential for the prevention of secondary complications
4. Realistic goals, reasonable expectations and a strong relationship with the patients are necessary for adequate compliance/adherence to therapy
# Common Etiologies of Neuropathic Pain

**Alcohol**

**Diabetes mellitus type 1 and 2**

Eosinophilia-myalgia syndrome
Guillain-Barre syndrome

**Heavy metals**

Arsenic
Lead
Mercury
Thallium

**HIV/AIDS**

**Malignancy (tumor-related)**

Monoclonal gammopathies
Multiple sclerosis
Post-stroke central pain
Postherpetic neuralgia

**Trauma:**

Carpal tunnel syndrome
Cervical or lumbar radiculopathy
Complex regional pain syndrome
Spinal cord injury
Stump pain

**Medications:**

Amiodarone, aurothioglucose, cisplatinum, dapsone, disulfiram, hydralazine, isoniazid, metronidazole, nitrofurantoin, paclitaxel, phenytoin, vincristine

Trigeminal neuralgia
Vasculitis
Vitamin B6 mega-dosing

**Vitamin deficiencies (B12, B1, B6, E)**

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Scales for the assessment of neuropathic pain

1. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
2. Neuropathic Pain Scale
3. Neuropathic Pain Questionnaire
4. Brief Pain Inventory for diabetic peripheral neuropathy

Neuropathy Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how sweet a piece of pie might be (the intensity of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the intensity of a sensation is not the same as how it makes you feel. A sound might be pleasant and still be loud (think of someone grating their fingernails on a chalkboard). A sound can be quiet and “dull” or loud and “dull.”

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, how much it hurts and how unpleasant or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.
### Neuropathic Pain Scale

1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain</td>
</tr>
<tr>
<td>1</td>
<td>Slight pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain</td>
</tr>
<tr>
<td>4</td>
<td>The most intense pain imaginable</td>
</tr>
</tbody>
</table>

2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a searing" "shooting," or "like sticks."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not sharp</td>
</tr>
<tr>
<td>1</td>
<td>Slight sharp pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sharp pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe sharp pain</td>
</tr>
<tr>
<td>4</td>
<td>The most sharp sensation imaginable</td>
</tr>
</tbody>
</table>

3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not hot</td>
</tr>
<tr>
<td>1</td>
<td>Slight hot pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate hot pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe hot pain</td>
</tr>
<tr>
<td>4</td>
<td>The most hot sensation imaginable</td>
</tr>
</tbody>
</table>

4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull thud," "dull pain," "aching," and "like a bruise."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not dull</td>
</tr>
<tr>
<td>1</td>
<td>Slight dull pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate dull pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe dull pain</td>
</tr>
<tr>
<td>4</td>
<td>The most dull sensation imaginable</td>
</tr>
</tbody>
</table>

5. Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not cold</td>
</tr>
<tr>
<td>1</td>
<td>Slight cold pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate cold pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe cold pain</td>
</tr>
<tr>
<td>4</td>
<td>The most cold sensation imaginable</td>
</tr>
</tbody>
</table>

### Neuropathic Pain Scale

6. Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not sensitive</td>
</tr>
<tr>
<td>1</td>
<td>Slight sensitive pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sensitive pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe sensitive pain</td>
</tr>
<tr>
<td>4</td>
<td>The most sensitive sensation imaginable</td>
</tr>
</tbody>
</table>

7. Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not itchy</td>
</tr>
<tr>
<td>1</td>
<td>Slight itchy pain</td>
</tr>
<tr>
<td>2</td>
<td>Moderate itchy pain</td>
</tr>
<tr>
<td>3</td>
<td>Severe itchy pain</td>
</tr>
<tr>
<td>4</td>
<td>The most itchy sensation imaginable</td>
</tr>
</tbody>
</table>

8. Which of the following best describes the time quality of your pain? Please check only one answer.

- [ ] I feel a background pain **all of the time** and occasional flare-ups (break-through pain) **some of the time.**
  
  Describe the background pain: ____________________________________________

  Describe the flare-up (break-through) pain: ________________________________

- [ ] I feel a single type of pain **all of the time.** Describe this pain:

- [ ] I feel a single type of pain only **sometimes.** Other times, I am pain free.

  Describe this occasional pain: ___________________________________________
Neuropathic Pain Scale

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "misery", "vast", and "intolerable". Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kind of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.

<table>
<thead>
<tr>
<th>Not unpleasant</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>The most unpleasant sensation imaginable (&quot;intolerable&quot;)</th>
</tr>
</thead>
</table>

10. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

**How intense is your deep pain?**

<table>
<thead>
<tr>
<th>No deep pain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>The most intense deep pain sensation imaginable</th>
</tr>
</thead>
</table>

**How intense is your surface pain?**

<table>
<thead>
<tr>
<th>No surface pain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>The most intense surface pain sensation imaginable</th>
</tr>
</thead>
</table>

Pharmacological Treatment of DPN
Table 1. Pharmacologic options with evidence from randomized clinical trials for efficacy in symptomatic treatment of DPNP (modified from Argoff et al. [113] with permission)

- First-tier agents (positive results from two or more randomized clinical trials)
  - Duloxetine (SNRI)
  - pregabalin (alpha2delta calcium channel modulator)
  - oxycodone CR (opioid)
  - TCAs (antidepressants)
  
- Second-tier agents (evidence of efficacy from a single trial in patients with DPNP and evidence from studies of other painful neuropathies)
  - gabapentin (alpha2delta calcium channel modulator)
  - celecoxib (SNRI)
  - tramadol (opioid)

Carbamazepine and lamotrigine may also be considered.

Topical therapies (based on mechanism of action, may be appropriate early in treatment and for specific indications)
- capsaicin
- lidocaine 5% patch

Some patients may require therapy with multiple agents. Multidrug decisions should be based on mechanism of action and adverse effect profiles.

Tier 1 Agents

- First-tier agents (positive results from two or more randomized clinical trials)
  - duloxetine (SNRI)
  - pregabalin (alpha2delta calcium channel modulator)
  - oxycodone CR (opioid)
  - TCAs (antidepressants)

Of these, duloxetine and pregabalin have FDA approval for treatment of DPNP.

Duloxetine (Cymbalta)

- FDA approved for treatment of depression and diabetic neuropathy
- Mechanism of Action
  - Balanced dual reuptake inhibitor of serotonin and norepinephrine
Duloxetine (Cymbalta)

- Pharmacokinetics
  - $t_{1/2}$: 8-17 hours: average 12 hours
  - Likely to be a substrate and moderate inhibitor of CYP2D6
    - 2D6 inhibitors: fluoxetine, paroxetine
  - Also metabolized by CYP1A2
    - Inhibitors of 1A2: Cimetidine, Cipro, Levofloxacin

- Dosing
  - Neuropathy: 60 mg qd (lower starting dose may be appropriate)
  - Available as 20, 30, 60 mg capsules [delayed release]
**Duloxetine: Adverse Events**

- Nausea (18-37%)
- Dry mouth (12-21%)
- Fatigue (9-11%)
- Constipation (7-11%)
- Dizziness (5-12%)
- Insomnia (3-12%): initially take in the AM
- Somnolence (4-5%)

*Difference from placebo; †Causing discontinuation

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**Duloxetine vs Placebo: General Pain Efficacy**

[Graph showing changes in pain scores over weeks for placebo and different Duloxetine doses.]
Duloxetine vs Placebo: Multidimensional Pain Efficacy

Lyrica® (Pregabalin)

- Mechanism of Action
  - Possibly due in part to:
    - Increased GABA content of neuronal tissues; GABA analogue
    - Binding to alpha₂delta subunit of calcium channels
    - Enhanced activity of glutamic acid decarboxylase
Lyrica® (Pregabalin)

- Absorption
  - Highly absorbed orally (90%)
- Elimination
  - 98% excreted unchanged in the urine
- Half-life: ~6 hours

Lyrica® (Pregabalin)

- Adverse Events
  - Dizziness
  - Somnolence
  - Peripheral edema
  - Weight gain
- Precautions
  - Possibility of myoclonus in epileptic patients
- Dosing
  - Initiate at 300-600mg/day
### Pregabalin: Frequently Occurring Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pregabalin (300mg/day, n=76)</th>
<th>Placebo (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>27 (35.5)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (19.7)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (14.5)</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>8 (10.5)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (7.9)</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (6.6)</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>4 (5.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4 (5.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>3 (3.9)</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (3.9)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (3.9)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (3.9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>3 (3.9)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3 (3.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3.9)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>


### Pregabalin vs Placebo on Neuropathic Pain

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Pregabalin (n=89)</th>
<th>Placebo (n=84)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean Pain Score</td>
<td>6.4 ± 1.5</td>
<td>6.3 ± 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean Pain Score</td>
<td>3.6 ± 0.24</td>
<td>5.29 ± 0.24</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Pain reduction of ≥30%</td>
<td>63%</td>
<td>25%</td>
<td>0.001</td>
<td>2.7</td>
</tr>
<tr>
<td>Pain reduction of ≥50%</td>
<td>50%</td>
<td>20%</td>
<td>&lt;0.05</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Dworkin et al. *Neurology* 2003; 60: 1274-1283
**Oxycodone CR (Oxycontin)**

- 10/15/20/30/40/60/80 mg
- Bioavailability: 60-85%
- Onset within 1 hour
- No ceiling effect
- Q 12 H dosing (sometimes dosed TID)
- No significant active metabolites
- SE’s: Constipation and Sedation

**Amitriptyline (Elavil)**

Mechanism of action of tricyclic antidepressants

[Diagram showing the mechanism of action of tricyclic antidepressants]
Amitriptyline Dosing

• Diabetic Peripheral Neuropathy:
  – 10-25mg QD
  – Titrate weekly by 10-25mg PRN
  – Max dose = 300mg/day

Desipramine (Norpramin) Dosing

- Diabetic Peripheral Neuropathy:
  - 10-25mg QD
  - Titrate weekly by 10-25mg PRN
  - Max dose = 300mg/day

Doxepin (Sinequan) Dosing

- Diabetic Peripheral Neuropathy:
  - 10-25mg QD
  - Titrate weekly by 10-25mg PRN
  - Max dose = 300mg/day

**Imipramine (Tofranil) Dosing**

- Diabetic Peripheral Neuropathy:
  - 10-25mg QD
  - Titrate weekly by 10-25mg PRN
  - Max dose = 300mg/day

**Nortriptyline (Pamelor) Dosing**

- Diabetic Peripheral Neuropathy:
  - 10-25mg QD
  - Titrate weekly by 10-25mg PRN
  - Max dose = 300mg/day
Tier 2 Agents

- Second-tier agents (evidence of efficacy from a single trial in patients with DPN and evidence from studies of other painful neuropathies)
  - gabapentin (alpha2delta calcium channel modulator)
  - venlafaxine (SNRI)
  - tramadol (opioid)
  - Carbamazepine and lamotrigine may also be considered.

Gabapentin (Neurontin)
Gabapentin Dosing

- Diabetic Peripheral Neuropathy:
  - 300mg QD on day 1, 300mg BID on day 2, then 300mg TID on day 3
  - Titrate by 100mg Q3 days PRN
  - Max dose = 3,600mg/day (TID or QID)

Gabapentin Adverse Reactions

**COMMON**
- Somnolence
- Dizziness
- Fatigue
- Tremor
- Weight Gain
- Nausea/Vomiting

**SERIOUS**
- Suicidal ideation
- Accumulation with impaired renal function
Venlafaxine (Effexor)

- How it Works:
  - Inhibition of serotonin and norepinephrine re-uptake
Venlafaxine Dosing

- Diabetic Peripheral Neuropathy:
  - 37.5-75mg QD
  - Usual maximum dose = 75mg BID for regular release; 150mg QD for ER
  - Higher doses may be necessary in some patients – titrate to clinical response

Venlafaxine Adverse Reactions

**COMMON**
- Dizziness
- Xerostomia
- Drowsiness
- Diaphoresis
- Increases in BP

**SERIOUS**
- Cardiac dysrhythmias
- Severe skin reactions
- Psychiatric changes
Carbamazepine (Tegretol)

How it Works:
- Carbamazepine blocks use-dependent sodium channels, inhibiting sustained repetitive firing
- Carbamazepine reduces post-tetanic potentiation of synaptic transmission in the spinal cord
Carbamazepine Dosing

- Diabetic Peripheral Neuropathy:
  - 100mg QD-BID
  - Titrate by 100mg/day at weekly intervals
  - Max dose = 1200mg/day

Carbamazepine Adverse Reactions

**COMMON**
- Dizziness
- Drowsiness
- Unsteadiness
- Nausea/Vomiting
- Edema

**SERIOUS**
- Bone marrow depression
- Skin reactions
- Exacerbation of CHF
Lamotrigine (Lamictal)

- How it Works:
  - May stabilize neuronal membranes by acting at voltage-sensitive sodium channels

Lamotrigine Dosing

- Diabetic Peripheral Neuropathy:
  - 50mg QD x 2 weeks, then 50mg BID x 2 weeks
  - Titrate by 100mg/day at 1-2 week intervals
  - Max dose = 700mg/day
Lamotrigine Adverse Reactions

**COMMON**
- Dizziness
- Drowsiness
- Blurred vision
- Weakness
- Nausea/Vomiting
- Insomnia

**SERIOUS**
- Suicidal Ideation
- Severe skin reactions
- Blood dyscrasias
- Hyponatremia

---

**Topical Agents**

- Topical therapies (based on mechanism of action, may be appropriate early in treatment and for specific individuals)
  - capsaicin
  - lidocaine 5% patch

Some patients may require therapy with multiple agents. Multidrug decisions should be based on mechanism of action and adverse event profiles.
Lidocaine (Lidoderm)

How it Works:
- Produces its analgesics effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium
- Loss of nerve function clinically is as follows: pain, temperature, touch, proprioception, skeletal muscle tone

Lidocaine Patch Dosing

- Diabetic Peripheral Neuropathy:
  - Apply to intact skin, cover most painful area.
  - Apply up to 3 patches for up to 12 hours within a 24 hour period
  - Patches may be cut before removal of liner
**Lidocaine Adverse Reactions**

**COMMON**
- Application site reactions
  - Pruritus
  - Burning
  - Erythema
  - Edema

**SERIOUS**
- Allergic reaction
- Exfoliation at patch site

**Capsaicin**

- How it Works:
  - Depletes and prevents re-accumulation of substance P in peripheral sensory neurons
Capsaicin Dosing

- Diabetic Peripheral Neuropathy:
  - Several controlled studies have shown capsaicin 0.075% topical cream to more effective than placebo
  - Was applied QID topically
Clonidine (Catapres)

How it Works:
Agonist at presynaptic alpha-2 receptors in the medulla, which results in inhibition of sympathetic outflow

Clonidine

- FDA Approved Indications:
  - Hypertension
  - Severe Pain

- Select Non-FDA Approved Indications
  - ADHD
  - Autism
  - Tourette’s Syndrome
Clonidine Dosing

• Diabetic Peripheral Neuropathy:
  • Initially 0.1mg PO QHS titrated upward 0.1mg/week PRN to a recommended maximum dose of 2.4mg/day

Clonidine Adverse Reactions

**COMMON**
- Dizziness
- Sedation
- Constipation
- Xerostomia
- Local skin reactions with patches

**SERIOUS**
- Orthostatic Hypotension
- Abrupt withdrawal can result in severe rebound hypertension

Mexiletine

- How it Works:
  - Inhibits fast sodium channels decreasing the rate of rise and amplitude of the action potential
  - = Oral congener of lidocaine
Mexiletine Dosing

• Diabetic Peripheral Neuropathy:
  – 200mg Q8h
  – Titrated 50-100mg Q2-3 days PRN
  – Max dose = 1200mg/day

Mexiletine Adverse Reactions

COMMON
• GI distress
• Dizziness
• Tremor
• Ataxia

SERIOUS
• Seizures
• Hallucinations
• Blood dyscrasias
• Arrhythmias
NSAIDs

- NSAIDs can often be used with success in patients with DPN
  - Affordable and easy to obtain
  - Be aware of any contraindications to therapy prior to recommending NSAID use

Summary of Studies for Pharmacotherapy Options

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Design</th>
<th>Dosing Schedule</th>
<th>Duration</th>
<th>Primary Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbano et al. (2004)</td>
<td>56</td>
<td>OPL, no control group</td>
<td>Daily application of up to 4 patches —18 hours on 6 hours off qd</td>
<td>3 weeks</td>
<td>Brief Pain Inventory (0 – 10): 6.4 → 3.6* 8-HTMPSU (0 – 45): 14.0 → 8.3*</td>
<td>ADR: burning (1), rash (1), photosensitivity (1)</td>
</tr>
<tr>
<td>Aneu et al. (2003)</td>
<td>120</td>
<td>R, RB, PC, PG</td>
<td>1 week PRO, then 600 mg IV qd over 30 minutes, 3 days/week for 14 doses</td>
<td>4 weeks</td>
<td>Total Symptom Score: 5.7 vs. 1.8 for PBO</td>
<td>ADE: none related to study drug</td>
</tr>
</tbody>
</table>

**Table 4**

**Summary of Selected Studies of Miscellaneous Agents for the Treatment of PDN**

**Design:**
- OPL: Opioid Patch Only
- PRO: Patch-Related Opioid
- 8-HTMPSU: Eight-Hour Tolerated Maximum Pain Score

**Primary Outcomes:**
- Brief Pain Inventory (0 – 10)
- 8-HTMPSU (0 – 45)

**Adverse Events:**
- ADR: burning, rash, photosensitivity

Table 3

Selected Analgesic Studies for the Treatment of PDN

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Design</th>
<th>Dosing Schedule</th>
<th>Duration</th>
<th>Primary Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girdle[1]</td>
<td>150</td>
<td>N, R, DB, PC, PG</td>
<td>10 – 60 mg bid (titrated to optimal dose by patient)</td>
<td>6 weeks</td>
<td>Opiodone CR</td>
<td>ADR: nausea (36%) vs. placebo, constipation (5%), vomiting (3%)</td>
</tr>
<tr>
<td>Whitton[2]</td>
<td>48</td>
<td>R, DB, CO, active PBO</td>
<td>10 – 60 mg bid (titrated to optimal dose)</td>
<td>8 weeks</td>
<td>VAS, pain (50)</td>
<td>ADR: nausea (30%) vs. placebo</td>
</tr>
<tr>
<td>Harris[3]</td>
<td>131</td>
<td>N, R, DB, PC, PG</td>
<td>Days 1 – 7: 50 – 200 mg/day; 100 mg increments qd, then qid by patient up to 400 mg/day, then final dose for 2 weeks</td>
<td>6 weeks</td>
<td>Tramadol</td>
<td>ADR: nausea (18%), vomiting (5%), constipation (10%), headache (16.9%)</td>
</tr>
<tr>
<td>Cramer[4]</td>
<td>18</td>
<td>Single-blind, PC, CO</td>
<td>Single 0.06 mgclid, then FBO, then sodium 20 mg, then placebo 20 mg each for 3 weeks</td>
<td>24 weeks</td>
<td>NSAID</td>
<td>ADR: nausea (29%), constipation (12%), headache (5%), vomiting (3%)</td>
</tr>
</tbody>
</table>

M = multicenter, R = randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, CO = crossover, PRO = placebo,

* Denotes statistically significant difference compared to placebo.

Table 2
Selected Antidepressant Studies for the Treatment of PNP

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Double-blind</td>
<td>6 months</td>
<td>10 mg/day</td>
<td>20 mg/day</td>
<td>Decreased pain severity</td>
</tr>
<tr>
<td>Study 2</td>
<td>Randomized</td>
<td>12 weeks</td>
<td>15 mg/day</td>
<td>30 mg/day</td>
<td>Improved mood</td>
</tr>
<tr>
<td>Study 3</td>
<td>Open-label</td>
<td>9 months</td>
<td>20 mg/day</td>
<td>Placebo</td>
<td>Reduced anxiety</td>
</tr>
</tbody>
</table>

Notes:
- PNP: Painful Neuropathy
- Double-blind: Participants and investigators do not know who is receiving which treatment.
- Randomized: Participants are assigned randomly to different treatment groups.
- Open-label: Both participants and investigators know who is receiving which treatment.

References:
### Table 1

**Summary of Selected Anticonvulsant Studies for the Treatment of PDN**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Design</th>
<th>Dosing Schedule</th>
<th>Duration</th>
<th>Primary Outcome</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rackeo et al. (2000)</td>
<td>223</td>
<td>M, R, D, PC</td>
<td>25 mg → 400 mg/day, max tolerated over 8 weeks, then final dose for weeks 8-12, mean maintenance dose: 325 mg</td>
<td>12 weeks</td>
<td>VAS: 84 → 46.2 vs. 69.1 → 54 mm for PBO*</td>
<td>ADR: 17/0.14 (80%) vs. 77/0.1% (71%) for PBO Withdrawal: 15/1.4% (41%) vs. 29/0.6% (7%) for PBO</td>
</tr>
<tr>
<td>Thienen (2004)</td>
<td>1,259</td>
<td>M, R, D, PC</td>
<td>25 mg → 100, 200, or 400 mg/d, over 6–18 weeks, then final dose for 12 weeks</td>
<td>18–22 weeks</td>
<td>VAS: 1 of the 3 trials showed significant benefit vs. PBO</td>
<td>ADR: Withdrawal: 24% vs. 8% for PBO Withdrawal: 46/1.8% vs. 53% vs. 158/3.1% (41%) for PBO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Eisenberg (2001)</td>
<td>59</td>
<td>R, DB, PC, P3</td>
<td>21 mg for 2 weeks, 50 mg for 2 weeks, then 100, 200, 300, 400 mg each for 1 week</td>
<td>5 weeks</td>
<td>NRS: 6.4 → 4.2 vs. 6.3 → 3 for PBO at 2/27 vs. 5/27 for PBO*</td>
<td>ADR: 1/26 for PBO</td>
</tr>
<tr>
<td>Kodakari (2004)</td>
<td>40</td>
<td>R, D, PC</td>
<td>500 mg/day for 1 week, then 500 mg bid for 1 month</td>
<td>13 weeks</td>
<td>VAS: 6 → 3 vs. 6 → 6 for PBO* SF-MPC: 19.37 → 9.66 vs. 17.76 → 17.88 for PBO*</td>
<td>ADR: 1.02 withdrawn for LT16</td>
</tr>
<tr>
<td>Kodakari (2005)</td>
<td>52</td>
<td>R, D, PC</td>
<td>200 mg tid for 1 week, then 400 mg tid</td>
<td>4 weeks</td>
<td>SF-MPC: 5.0 → 3.41 vs. 4.5 → 4.0 for PBO*</td>
<td>ADR: 1.25 withdrawn for LT16</td>
</tr>
<tr>
<td>Mullan (1989)</td>
<td>30</td>
<td>DB, PC, CO</td>
<td>Active: 200 mg → 400 mg over 3 weeks</td>
<td>5 weeks</td>
<td>Improvement in self-reported pain intensity; 28/30 vs. 19/30 for PBO*</td>
<td>ADR: somnolence (50%), dizziness (45%)</td>
</tr>
<tr>
<td>Reynders (2004)</td>
<td>30</td>
<td>OL</td>
<td>110 mg/day → 390–1,260 mg/day over 4 weeks, the final dose for 4 weeks</td>
<td>4 weeks</td>
<td>VAS: 56.3 → 34.3* &gt;50% vs. 14.39*</td>
<td>ADR: dizziness (13/63), dizziness (1/63)</td>
</tr>
</tbody>
</table>

M = medication; R = randomized; D = double-blind; PC = placebo-controlled; PC = parallel-group; CO = crossover; OL = open label; PBO = placebo; VAS = visual analog scale; SF-MPC = scores from McGill pain questionnaire. NRS = numerical rating scale. PPI = pain intensity. ADR = adverse drug reaction. LT = loss to follow-up.

* Denotes statistically significant difference.
Alternative Therapies for the Treatment of DPN
**Alpha-Lipoic Acid**

- Proposed MOA—improved blood flow to peripheral nerves
- Scientific evidence/efficacy—evidence suggests ALA is likely effective for diabetic neuropathy, however, results are inconclusive and variable
- Goal—stimulate nerve fiber regeneration
- Dosing
  - 600-1200mg daily PO or IV have shown greatest benefit in studies where symptoms were reduced/improved
  - Recommended effective dose: 600mg daily
  - Targeted symptoms—appears to improve sensory symptoms (burning, tingling, numbness, pain) and ratings of neurological deficit and disability

**Alpha-Lipoic Acid**

- Onset of symptom relief—3 to 5 weeks with both PO and IV administration
- Adverse effects—can potentially lower blood glucose (need to monitor)
  - PO—nausea, vomiting, abdominal pain, skin rash, HA
  - IV— injection site reaction
- Drug-drug interactions
  - Oral hypoglycemic medications or insulin ↔ ALA: may have additive hypoglycemic effects
- Clinical pearl: Best absorbed if taken on an empty stomach

Source: Natural Medicines Comprehensive Database
• Typical B Complex: Vitamin B6 50.0 mg Folate 400.0 mcg Vitamin B12 50.0 mcg
• L-methylfolate 2.8mg (active metabolite of folic acid), pyridoxal 5’-phosphate 25mg (active metabolite of vitamin B6), methylcobalamin 2mg (active metabolite of vitamin B12)

Indication: Hyperhomocysteinemia, which is a result of deficiencies in folic acid, B6 and B12

Benefits over OTC supplements:
– ~10% of people cannot metabolize folic acid to L-methylfolate
– ~40% only convert a limited amount of folic acid to L-methylfolate
METANX

• Onset of relief is 1 week to 4 months, depending on the individual
• Prescription only
• If insurance doesn’t cover, 20% off discount card available from mfg website
• Pyridoxal 5’-phosphate is “slightly better absorbed” than pyridoxine hcl (the form in most OTC B-vitamins)
• Most OTC B-vitamins contain cyanocobalamin, but there are products available that have methylcobalamin instead
• Cost: $70/60 tablets (per Rite Aid) vs. $3-10/100 tablets OTC (per www.walgreens.com)

Acetyl-L Carnitine

• Possibly effective in patients with DPN
• Improvements observed in patients following treatment with 1500-3000mg daily in divided doses for 1 year
  • Possible regeneration of nerve fiber clusters and improvement in vibratory sensation
  • Appears more effective in patients with a shorter duration of diabetes, and in patients with poorly-controlled T2DM

Source: Natural Medicines Comprehensive Database
**Gamma Linolenic Acid**

- Possibly effective in patients with DPN
  - Oral administration for 6-12 months has demonstrated reduced symptoms and prevention of neurological deterioration in patients with DPN (both type 1 and 2 diabetes)
    - Appears in studies to be more effective in patients with better glucose control compared to those with poor control

Source: Natural Medicines Comprehensive Database

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**Biotin**

- Insufficient reliable evidence to validate efficacy for the treatment of DPN
  - Preliminary evidence exists that intramuscular or oral biotin may help decrease symptoms associated with DPN --- More evidence is needed

Source: Natural Medicines Comprehensive Database
**Vitamin C?**

• Early data indicate that ascorbic acid functions as an aldose reductase inhibitor
• May slow the progression of DPN through action on the polyol flux pathway

**Magnet Therapy**

• Possibly effective for DPN:

  Some clinical research indicates that wearing a shoe insole containing a static magnet can reduce symptoms of burning, numbness, tingling, and exercise-induced foot pain after 3-4 months of treatment compared to placebo

Source: Natural Medicines Comprehensive Database
**Possible treatment for Peripheral Neuropathy**

“Pineapple Cocktail”

- 2 slices of fresh raw pineapple
- 2 carrots
- 1 orange

Blend, and enjoy before bedtime!
Thank You!

Special Thanks to:

Josh Neumiller, PharmD
Kristine Large, PharmD
Jeanette Bidondo, PharmD

Questions? / Comments!