Diabetes-Related Peripheral Neuropathy

Jessica L. Kerr, PharmD, CDE
Associate Professor – SIUE School of Pharmacy
Clinical Pharmacist – Belleville CBOC VAMC

Christopher Herndon, PharmD, BCPS, CPE
Associate Professor – SIUE School of Pharmacy
Clinical Pharmacist – Southern Illinois Healthcare Foundation
Objectives

• Describe the pathophysiologic mechanisms for Painful Diabetes Peripheral Neuropathy (PDPN)

• Identify treatment options and discuss pharmacology, monitoring and clinical pearls regarding these treatment modalities

• Discuss clinical practice guidelines

• Evaluate current evidence to solidify treatment options

• Outline the diabetes educator’s role
Epidemiology

• Most common and costly complication of diabetes
• 8-10% of cases may be present at diagnosis
• Greater than 50% have chronic PDPN
• Largely unreported/untreated

• Annual cost of $10.9 billion associated with DPN
Prevalence “Risk”

- Duration of diabetes
- Level of glycemic control
- Age
- T2DM > T1DM
Definition on Painful Diabetic Peripheral Neuropathic Pain

- “Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”
  - International Association for the Study of Pain

# Types of Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Diffuse Neuropathy</th>
<th>Focal Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic AUTONOMIC Neuropathy (DAN)</strong></td>
<td>• Mononeuropathy</td>
</tr>
<tr>
<td>• Abnormal pupillary function</td>
<td>• Mononeuropathy multiplex</td>
</tr>
<tr>
<td>• Sudomotor dysfunction</td>
<td>• Plexopathy</td>
</tr>
<tr>
<td>• Genitourinary</td>
<td>• Radiculopathy</td>
</tr>
<tr>
<td>• Gastrointestinal</td>
<td>• Cranial neuropathy</td>
</tr>
<tr>
<td>• Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>• Hypoglycemia unawareness</td>
<td></td>
</tr>
<tr>
<td><strong>Distal Symmetrical Sensorimotor Polyneuropathy (DPN)</strong></td>
<td></td>
</tr>
<tr>
<td>• Small fiber</td>
<td></td>
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<tr>
<td>• Large fiber</td>
<td></td>
</tr>
<tr>
<td>• Mixed</td>
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Clinical Presentation

• Typical DPN
  • Symmetrical, length-dependent sensorimotor
  • Most common
  • Long standing hyperglycemic state

• Atypical
  • May develop at any course of diabetes
  • Onset may be acute, subacute or chronic
  • Monophasic or fluctuating
  • Pain and autonomic symptoms are typically featured

## Typical Neuropathic Symptoms

<table>
<thead>
<tr>
<th>Painful</th>
<th>Nonpainful</th>
</tr>
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<tbody>
<tr>
<td>Burning pain</td>
<td>Numbness</td>
</tr>
<tr>
<td>Knife-like</td>
<td>Tingling</td>
</tr>
<tr>
<td>Electrical sensations</td>
<td>Prickling</td>
</tr>
<tr>
<td>Squeezing</td>
<td>Asleep</td>
</tr>
<tr>
<td>Constricting</td>
<td>“Dead”</td>
</tr>
<tr>
<td>Hurting</td>
<td></td>
</tr>
<tr>
<td>Freezing</td>
<td></td>
</tr>
<tr>
<td>Throbbing</td>
<td></td>
</tr>
<tr>
<td>Allodynia</td>
<td></td>
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Diagnosis of PDPN

- Thorough history
  - OPQRST
- Neurologic exam
  - Pinprick
  - Temperature
  - Vibration sensation
  - 10 gram monofilament test
  - Distal reflexes
- Rule out other frequent causes
  - B_{12} deficiency, hypothyroidism, uremic syndrome, peripheral vascular disease
- Electrophysiological testing not routinely recommended
  - Nerve conduction velocity studies
  - Quantitative Sensory Testing

## Screening Tools

<table>
<thead>
<tr>
<th>Sensation</th>
<th>ID Pain</th>
<th>NPQ</th>
<th>Pain DETECT</th>
<th>LANSS</th>
<th>DN4</th>
<th>StEP</th>
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</thead>
<tbody>
<tr>
<td>Dysesthesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Electrical, shock, or shooting</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hot / burning</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Allodynia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold-evoked</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Heat or cold-evoked</td>
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<td></td>
<td></td>
<td></td>
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<td>+</td>
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<tr>
<td>Weather related</td>
<td>+</td>
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<tr>
<td>Itching</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Autonomic changes</td>
<td>+</td>
<td></td>
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# Assessment of Pain

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<tr>
<th>Neuropathic Pain Rating Scale</th>
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<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>
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</thead>
<tbody>
<tr>
<td>No Pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Not sharp</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
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<tr>
<td>Not hot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
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<tr>
<td>Not dull</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
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<tr>
<td>Not cold</td>
<td>0</td>
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<td>3</td>
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<tr>
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<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Not itchy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Not unpleasant</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No surface pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No deep pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
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I feel a background pain all of the time and occasional flare-ups (break-through pain) some of the time (Describe)
I feel a single type of pain all of the time (Describe)
I feel a single type of pain only sometimes. Other times I am pain free

**Proposed Pathogenesis of PDPN**

**Metabolic**
1. Accumulation of glycosylation end products
2. Protein kinase C disruption
3. Increased oxidative stress
4. Loss of insulin-mediated neurotrophic repair

**Brain**
1. Thalamic dysfunction likely due to deafferentation
2. Aberrant spontaneous thalamic activity

**Spinal Cord**
1. Significant cord shrinkage at C2/C3 level
2. Cord area correlated with severity of PDPN
3. TRPV1 downregulation
4. CB1 upregulation

**Peripheral**
1. VSSC distribution and expression
2. VSCC distribution and expression
3. Microglial activation
4. Neuropeptide upregulation
5. Primary afferent sprouting
6. Recruitment of silent nociceptors
7. Axonal degeneration, atrophy, and aberrant regeneration

**Central**
1. Faulty synapse into superficial laminae of the dorsal horn
2. Disinhibition via cascade of decreased GABA, noradrenergic, and serotonergic neurotransmitters

**Vascular**
1. Microvascular basement membrane thickening
2. Endothelial cell proliferation
3. Endothelial cell hypertrophy
4. Microvascular arteriosclerosis

**Neuropathy**
- Allodynia
- Hyperalgesia

**References**
Neuroplasticity

• Functional and structural alterations in the nervous system.
  • Up-regulation of Na\(^{++}\) channels leading to ectopic AP activity from the periphery
  • Reorganization of synaptic connections in dorsal horn of spinal cord
  • Loss of both pre & post-synaptic inhibition
    • Facilitation
    • Central sensitization

Allodynia and Dysesthesia

Dorsal Horn
Elevator Analogy

Laminae I & II: pain
Laminae III: touch
Laminae V: WDRN (pain & touch)
Allodynia

alpha-beta (light touch)

Sprout

Laminae III

Laminae II

Laminae I
Meet Lucinda

- LM is a 65 year old female with a 15 year history of Type 2 DM. Her last HgbA1c was 6.4 maintained on metformin and insulin glargine.
  - PMH: HTN, hyperlipidemia, tob abuse,
  - Vitals: BP is 136/96mmHg
  - Labs: TC 280mg/dl, HDL 42mg/dl, LDL 110mg/dl, Trig 290mg/dl
  - Comprehensive metabolic panel normal
  - Meds: lisinopril, metformin, atorvastatin, and insulin glargine

- Issues with tingling pain symmetrically in all lower extremity digits with burning sensations worse at night. Allodynia evoked by bed sheets.

- Upon PE: (-) perception of vibration bilaterally, skin color and temperature abnormalities
Guideline Driven Treatment

American Academy of Neurology; American Academy of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation; European Federation of Neurological Societies

- Difference in the proportion of patients reporting greater than 30-50% from baseline

- Percent change from baseline on scales

- Other quantitative measure of pain utilized by investigators

Guideline Driven Treatment

American Academy of Neurology; American Academy of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation; European Federation of Neurological Societies

- Difference in the proportion of patient reporting greater than 30-50% from baseline
  - LARGE EFFECT: risk difference of > 20% (NNT < 5)
  - MODERATE EFFECT: risk difference of 10-20% (NNT 5-10)
  - SMALL EFFECT: risk difference ≤ 10% (NNT > 10)
Guideline Driven Treatment
American Academy of Neurology; American Academy of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation; European Federation of Neurological Societies

- Percent change from baseline on scales
  - LARGE EFFECT: > 30%
  - MODERATE EFFECT: 15-30%
  - SMALL EFFECT: ≤15%
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American Academy of Neurology; American Academy of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation; European Federation of Neurological Societies

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<td></td>
<td>Venlafaxine, Duloxetine, Amitriptyline</td>
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<td>Pregabalin</td>
<td>Gabapentin, Sodium Valproate</td>
<td>Oxcarbazepine, Lamotrigine, Lacosamide</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td>Tramadol, Oxycodone, Morphine</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Dextromethorphan, Capsaicin, Isosorbide Dinitrate</td>
<td>Clonidine, Pentoxifylline, Mexiletine</td>
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# Guideline Driven Treatment

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Recommended dosages

- Level A
  - Pregabalin, 300-600mg/dl*
- Level B
  - Gabapentin, 900-3600mg/d
  - Sodium Valproate, 500-1200mg/d
  - Venlafaxine, 75-225mg/d
  - Duloxetine, 60-120mg/d*
  - Amitriptyline, 25-100mg/d
  - Dextromethorphan, 400mg/d
  - Morphine sulfate, titrated to 120mg/d
  - Tramadol, 210mg/d
  - Oxycodone, mean 37mg/d, max 120mg/d
  - Capsaicin, 0.075% QID
  - Isosorbide dinitrate spray
  - Electrical stimulation, percutaneous nerve stimulation x 3-4 weeks
- *FDA Approved

Anticonvulsants

Antidepressants

Opioids
Treatment Options and Clinical Pearls

- Anticonvulsants
- Antidepressants
- Opioids
- Other
- Non-Pharm
Antidepressants with NE & 5HT Activity

- **TCAs (NE > 5HT)**
  - Amitriptyline
  - Imipramine
  - Desipramine
  - Nortriptyline
  - Clomipramine
  - Doxepin

- **SSRIs (5HT > NE)**
  - Paroxetine
  - Citalopram
  - Escitalopram

- **SNRIs (NE = 5HT)**
  - Venlafaxine
  - Desvenlafaxine
  - Duloxetine
  - Milnacipran

- **Atypicals**
  - Bupropion
  - Mirtazapine
  - Trazadone
  - Vilazadone

So which anticonvulsant?

- Non-obese, co-morbid anxiety
  - Gabapentin, pregabalin

- Obese, or co-morbid seizure disorder
  - Zonisamide, topiramate

- Co-morbid bipolar disorder or seizure disorder
  - Oxcarbazepine, carbamazepine, valproic acid, lacosamide?

Cochrane Collaborative and TIMI Bipolar Guidelines
Capsaicin

- Activates nerve fibers in the skin, which becomes desensitized over time as a result of depletion of substance P and calcitonin gene-related peptides (reversible nerve degeneration)

- Onset is 4 weeks for modest effect

- After therapy discontinued, epidermal nerve fibers are reinnervated over a 6 week period

- **Role may be limited to adjunctive therapy for mild pain**
  - Capsaicin NNT = 8.1
  - Topical NSAID NNT = 3.1

- Not associated with serious adverse events
  - Accidental contact with the eyes or mucus membranes is extremely irritating (Wash hands immediately after use)
  - Adverse event rate = 54% (vs. 15% placebo)

Lidocaine

• Topical anesthetic and Class 1b anti-arrhythmic

• Sodium channel blockade Na(v) 1.7

• Inhibition of Acid Sensing Ion Channels (ASIC)

• Available via OTC (0.5-4%) and prescription (5%)
  • OTC: Anestafoam®, Solarcaine®, LMX®, Anecream®, Lidamantle®, Topicaine®, Burn Jel®, Regenecare®, Unburn®, Band-Aid®
  • Rx: Lidoderm®, Hurricaine®, Xylocaine®

• Lidocaine 5% patch applied directly to area of PHN
• No more than 3 patches concurrently
• 12 hours on, 12 hours off

What would we recommend for Lucinda?

- LM is a 65 year old female with a 15 year history of Type 2 DM. Her last HgbA1c was 6.4 maintained on metformin and insulin glargine. PMHx includes HTN, HLP, tobacco abuse,

  VITALS: 136/96
  LAB: TC 280, HDL 42, LDL 110, Trig 290
  Comprehensive metabolic – normal
  MEDS: lisinopril, metformin, atorvastatin and insulin glargine.

- Issues with tingling pain symmetrically in all lower extremity digits with burning sensations worse at night. Allodynia evoked by bed sheets.

- Upon PE: (-) perception of vibration bilaterally, skin color and temperature abnormalities

Provider recommends starting therapy for Lucinda. What is the most appropriate first line agent specific for her?

Lucinda does not have prescription drug coverage, what could we trial?

When would we follow up with Lucinda to assess outcomes of current therapy recommended today?
What would we recommend for Lucinda?

- Three years have progressed and LM’s diabetes is controlled with A1c < 7%. She has trialed gabapentin and was not able to tolerate higher doses. Currently she is maxed out with pregabalin with some results of improved pain. She is interested in finding a greater level of pain control.

What are our options for the next step in therapy?

Is combination therapy recommended in refractory cases?
Non-Pharmacologic Treatment

- Stable and optimal glycemic control
  - Improvement of symptoms with intensive therapy
  - Improvement in nerve conduction velocity
  - Reduction in rate of progression
- Regular foot examinations
- Reversal of modifiable risk factors
- Interventional pain management
- Surgical nerve decompression

Complementary and Alternative Medicine Treatment

- Acupuncture
- Reiki Therapy
- Massage
- Magnetics
- Laser therapy
- Infrared therapy
- Neutra-ceuticals

Alpha-lipoic acid (ALA)

- Free radical scavenger
- 600mg daily
- Reductions in both
  - Blood glucose levels
  - Neuropathic pain on validated scales
- Primary drawback is reliable quantity in commercially available products

Acetyl-L-carnitine (ALC)

- Only 1000mg QD - TID found effective (not 500mg)
- Shunts carbohydrates to energy via Acetyl CoA vs. storage
- Mechanism in PDPN thought to be antioxidant in nature

B Vitamins

• Numerous marketed “remedies”
  • Vitamin B6 (pyridoxine) or pyridoxal 5’-phosphate
  • Vitamin B12 (cyanocobalamin) or methylcobalamin
  • Vitamin B9 (folate) or L-methylfolate

• Some expensive
• Easy to tolerate
• Small effect size, but benefit outweighs risk

Meet Michael

• A 62 yo Male with T1DM x 45 yrs. On insulin pump

• Complains of progressive DPN. Past Meds: gabapentin (not able to tolerate doses > 2700mg/dl due to insomnia), pregabalin (caused drowsiness), tramadol (without relief)

• A1c 8.2%, FLP (nl), CMP (nl), ^LFTs (fatty liver disease), B12 and TSH (nl), Wt: 189# Ht: 5’8”, (+) Smoker, routine BPs: 128/69mmHg
• What aspects of this patient’s care should be optimized to improve progression of DPN?

• What would be the next drug therapy you would recommend with a brief rationale?

• Would your recommend ALA or ALC for Michael and if so, what dose?
Diabetes Management SIG

The Diabetes Management Special Interest Group is a support network for pharmacists who share an interest in the area of diabetes management. The Diabetes Management SIG will allow pharmacists in this area of practice to connect with others in the field and provide opportunities to discuss up-to-date disease management information.
Accessing the Diabetes Management SIG

- APhA-APPMM Diabetes Management SIG Website: http://www.pharmacist.com/diabetes-management-sig
- APhA-APPMM Diabetes Management SIG e-Community: www.pharmacist.com
  - Instructions for accessing:
  - Login into pharmacist.com with your username and password
  - Click on “My Account”
  - Select “Academies, Sections, and SIGs” on the left side
  - Click on “Edit”
  - Under “Primary Academy” select “APhA-APPMM”
  - Under “APhA-APPMM Special Interest Groups (APhA-APPMM SIGs)” Check the box next to “SIG- Diabetes Management”
  - Once the above steps have been completed, you will be automatically be subscribed to the “Diabetes Management SIG”