Strategies for Managing Painful Diabetic Neuropathy

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Objectives:

• List the signs and symptoms associated with diabetic neuropathy, clinical assessments, and testing used to diagnose diabetic neuropathy.

• Given an actual or simulated case of a patient with diabetic neuropathy, list relevant patient and drug-related variables and recommend drug therapy to relieve pain.

• Given an actual or simulated case of a patient with diabetic neuropathy, monitor and adjust the therapeutic regimen, and counsel patient on medication management.

• Describe other management strategies (e.g., improved blood glucose control) and general patient education for a patient with diabetic neuropathy.

Program Overview:

Painful diabetic neuropathy (PDN) is a classic complication of diabetes. PDN refers to a chronic, often excruciating, refractory pain described as distal symmetrical sensorimotor polyneuropathy. This pain begins distally in the arms and legs, is usually symmetrical in nature, and often affects multiple nerve fibers. PDN affects approximately 10% of people with diabetes at the time of diabetes diagnosis, and between 30% and 50% of patients within 25 years. Participants in this presentation will learn about the risk factors for the development of PDN, the clinical assessment to detect and monitor this painful complication, severity staging and how to manage the complications. First, second and third line medication options will be discussed, including medication selection, dosing, monitoring, and adjustment.

Strategies for Managing Painful Diabetic Neuropathy

Speaker: Dr. Mary Lynn McPherson is a Professor in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy. She serves as a consultant pharmacist for both local and national hospice and palliative care programs, and has designed a critical thinking process for appropriate drug use in end of life patients. She serves on the Board of the Hospice Network of Maryland, chairing the Education and Outreach Committee. She also serves on the Board of the Maryland Pain Initiative and the Advisory Board of the American Society of Pain Educators.

Speaker Disclosure: Dr. McPherson has no actual or potential conflicts of interest in relation to this program.

Accreditation:

• Pharmacists: 0788-0000-10-042-L01-P
• Pharmacy Technicians: 0788-0000-10-042-L01-T
• Nurses: N018

Target Audience:

• Pharmacists
• Pharmacy Technicians
• Nurses

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Definition of Pain

- “...an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” The International Association for the Study of Pain (1979)
- Pain is subjective
- “Pain is what the person says it is, existing whenever he says it does.”
  Margo McCaffrey 1968

Nociceptive Pain
- Normal processing of stimuli that damages normal tissues, or has the potential to do so if prolonged
- Usually responsive to non-opioids and opioids

Neuropathic Pain
- Abnormal processing of sensory input by the peripheral or central nervous system;
- Treatment usually includes adjuvant analgesics

Neuropathic Pain
- Pain sustained by abnormal processing of sensory input by the peripheral or central nervous system
  - Results from injuries to CNS or peripheral nerves rather than stimulation of nerve endings
  - Pain occurs because injured nerves react abnormally to stimuli or discharge spontaneously
- Defined as:
  - “…painful syndromes that are initiated or caused by a primary lesion or dysfunction in the nervous system.”
- Characterized by:
  - Pain and sensory symptoms that persist beyond the healing period.
  - Presence, in variable degree, or neurological sensory signs manifesting as negative and positive sensory phenomena.
  - Presence, in variable degree, of other neurological signs, including motor, manifesting as negative and positive motor phenomena or autonomic signs.

Up to 4 million people in the United States suffer from chronic neuropathic pain conditions.

1Defined by International Association for the Study of Pain
2Backonja, Aneseth Analg 2003
Strategies for Managing Painful Diabetic Neuropathy

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Neuropathic Pain

- Neuropathic pain can be:
  - Stimulus-evoked (hyperalgesia, allodynia)
  - Spontaneous stimulus-independent
    - Constant, intermittent, or paroxysmal
- Spontaneous pain usually described as a constant burning plus intermittent pain
  - “shooting,” “electric-shock like”
  - Pain may be accompanied by spontaneous paresthesias and dysesthesias
- Stimulus-evoked pain may be caused by:
  - Light touch, pressure of clothing, wind, hot or cold temperatures

Assessing Neuropathic Pain

- Neuropathic Pain Questionnaire — Short Form
- Rating the most severe or disturbing pain, how it usually feels:
  - Tingling pain (0 is no tingling; 10 worst possible)
  - Numbness (0 is no numbness; 10 worst possible)
  - Increased pain due to touch (0 is no increase at all; 10 is greatest increase imaginable)

Backonja, Clinical J Pain 2003

Painful Diabetic Neuropathy

- Diabetes is defined as:
  - “...a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.
  - The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.”
- Painful diabetic neuropathy - PDN

Painful Diabetic Neuropathy

- Epidemiology
  - PDN affects 30% hospitalized diabetic patients and 20% community patients
  - Approximately 7% of patient have PDN at time of DM diagnosis; 50% within 25 years
  - About 4-5% of all patients with diabetes will have PDN
Painful Diabetic Neuropathy

- Risk factors for PDN
  - Sustained hyperglycemia
  - Duration of diabetes mellitus
  - Patient age
  - Cigarette smoking
  - Alcohol consumption
  - Hypertension
  - Height (taller patients at increased risk)
  - Hypercholesterolemia

DCCT showed 2% annual incidence vs. 0.65% annual incidence (control/intervention)

Painful Diabetic Neuropathy Pathogenesis

- Metabolic theory
  - Intracellular hyperglycemia in nerves results in saturation of the glycolytic pathway
  - Results in accumulation of sorbitol and fructose

- Vascular theory
  - Endoneurial ischemia develops due to increased vascular resistance

- Other theories
  - Impaired production and transport of nerve growth factor, lack of normal expression of laminin, and the development of autoimmune neuropathy

Stages of PDN

<table>
<thead>
<tr>
<th>Stage of neuropathy</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuropathy</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>Clinical neuropathy – chronic painful</td>
<td>Burning, shooting, stabbing pains with or without pins and needles; increased at night; absent sensation to several modalities; reduced/absent reflexes</td>
</tr>
<tr>
<td>Clinical neuropathy – acute painful</td>
<td>Severe symptoms as above (hyperesthesia common), may follow initiation of insulin in poorly controlled diabetes, signs minor or absent</td>
</tr>
<tr>
<td>Painless with complete/partial sensory loss</td>
<td>Numbness/deafness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensitivity, absent reflexes</td>
</tr>
<tr>
<td>Late complications</td>
<td>Foot lesions, neuropathic deformity, nontraumatic amputation</td>
</tr>
</tbody>
</table>

PDN Clinical Presentation

- Complaints of pain and paresthesia
  - Burning, tingling, aching, cold sensation, lancinating pain like walking on glass, numbness, pain from normal touch
- Complaints dysesthesia
  - “buzzing,” “like bugs crawling”
- Adversely effects sleep

PDN Clinical Presentation

- Negative sensory symptoms
  - Inability to feel, identify or manipulate smaller objects
  - Lose ability to judge temperature or sense painful stimuli
  - Unsteadiness in walking
- Descriptors include: asleep, “dead,” numbness, tingling, pricking
- Frequently depressed or anxious

Management of PDN

- Therapeutic goal
  - To prevent, or at least delay, progression to greater symptom severity (nerve fiber loss)
  - Achieve functional goals (e.g., able to sleep through night without pain, accomplish ADLs)
  - Prevent ulcers and amputations
- Strategies
  - Improve blood glucose control
  - Symptomatic management of the pain
  - Interventions to prevent onset or modify progression of PDN under investigation
Audience Response

- Which of the following is considered to be a “negative” sensory symptom associated with PDN?
  - A. Burning
  - B. Buzzing sensation
  - C. Unsteadiness in walking
  - D. Lancinating pain

Foot Care for DPN Patients

- Clean feet daily using warm water and mild soap; avoid soaking feet; dry with soft towel; carefully dry between toes.
- Inspect feet and toes twice daily for cuts, blisters, redness, swelling, calluses; use a mirror (try placing on floor) to inspect bottoms of feet if movement is limited.
- Moisturize feet with lotion, but avoid area between toes.
- After cleaning, file corns and calluses gently with pumice stone.
- Cut toenails regularly to the shape of your toes and file edges.
- Always wear shoes or slippers to protect feet from injuries; wear thick, seamless socks.
- Wear well-fitted shoes that allow toe movement; break in new shoes gradually.
- Before wearing shoes, check inside for tears, sharp edges, or objectives that might cause injury.
- Inform your physician if you notice any changes in the appearance of or any unusual sensations in your feet.

Therapeutic Options - PDN

- **SNRIs** – duloxetine (Cymbalta), venlafaxine (Effexor)
- **α,δ ligands** – pregabalin (Lyrica), gabapentin (Neurontin)
- **TCAs** – amitriptyline (Elavil), desipramine, nortriptyline
- **Opioids** – tramadol, oxycodone, morphine, methadone, hydromorphone
- **Topical agents** – capsaicin (Zostrix), lidocaine (Lidoderm)

**SNRI – Duloxetine (Cymbalta)**

- Evaluated in 2 RCTs, approved for PDN
- Recommended dose 60 mg/day
- When compared to placebo, duloxetine showed greater reduction in APS, and other measures
- AE greater with duloxetine: somnolence, constipation, nausea, dizziness, dry mouth, sweating, increased appetite, anorexia, weakness
### SNRI – Venlafaxine (Effexor)
- Studied in one RCT for PDN, and compared vs. imipramine for treatment of painful neuropathies
- Doses of 150-225 mg/day of venlafaxine ER significantly reduced pain intensity compared to placebo (and vs. lower dose venlafaxine)
- Most common AE: nausea, somnolence, dyspepsia, insomnia, sweating, impotence

### TCAs (amitriptyline, desipramine, nortriptyline)
- Widely used to treat neuropathic pain (not FDA approved however)
- No difference in efficacy among TCAs
- Amitriptyline best studied; RCT showed benefit
- Desipramine (vs. placebo, and vs. amitriptyline) – > placebo, = amitriptyline
- AE: dry mouth, constipation, dizziness, blurred vision, cardiac arrhythmias, urinary retention

### α₂δ ligand – Pregabalin (Lyrica)
- Studied in 3 RCT for PDN
- Doses of 300-600 qd significantly improved pain
- AE: weight gain, dizziness, somnolence, peripheral edema, confusion
- Increase efficacy seen at 600 mg/day may be offset by increased AE
- No known drug interactions; but TID dosing

### α₂δ ligand – Gabapentin (Neurontin)
- Studied in one RCT vs. placebo – showed improvement in pain rating
- Treatment up to 3600 mg/d significantly improve pain severity and improve sleep
- AE: somnolence, dizziness
- Appropriate second-tier choice in patients who do not respond to, or cannot tolerate first-tier agents
- Requires titrated dosing, and multiple daily doses
<table>
<thead>
<tr>
<th><strong>Opioids – Oxycodone CR (generic)</strong></th>
<th><strong>Tramadol (Ultram)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Generic long-acting oxycodone studies in 2 RCT for PDN: oxycodone reduced pain (average and worst rating)</td>
<td>• Centrally acting analgesic; weak inhibitor of NE/SHT reuptake and low affinity for mu receptor</td>
</tr>
<tr>
<td>• AE: constipation, somnolence, nausea, dizziness, pruritus, vomiting, dry mouth</td>
<td>• Shown to improve pain and physical functioning in PDN (did not improve sleep)</td>
</tr>
<tr>
<td>• Be mindful of possible warning signs of abuse</td>
<td>• AE: nausea, constipation, headache, somnolence, sweating, seizures</td>
</tr>
<tr>
<td>• Consider use of an opioid agreement</td>
<td>• Second-tier agent (AE and four times daily dosing, abuse/dependence concerns)</td>
</tr>
</tbody>
</table>

**Topical Agent – Capsaicin (Zostrix)**

- Active principle of hot chili pepper
- Causes the release and depletion of substance P; reduces/abolishes transmission of painful stimuli from peripheral nerve
- More effective than placebo vehicle
- AE: stinging, burning (especially early in tx)

**Topical Agent - Lidoderm**

- Commonly used in primary care to treat painful conditions
- Evaluated in a RCT with good effect
  - Pain ratings
  - Quality of life
- AE no difference compared to placebo; most commonly reported AE rash and pruritus
- FDA-approved for 12 hours on, 12 hours off
## Strategies for Managing Painful Diabetic Neuropathy

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<table>
<thead>
<tr>
<th>Agent Type</th>
<th>Reason for Recommendation</th>
<th>Agent Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>First tier</td>
<td>≥ 2 RCTs in DPN</td>
<td>Duloxetine (Cymbalta) Oxycodone (CR generic) Pregabalin (Lyrica) TCAs</td>
</tr>
<tr>
<td>Second tier</td>
<td>1 RCT in DPN; ≥ 1 in other painful neuropathies</td>
<td>Carbamazepine (Tegretol) Gabapentin (Neurontin) Lamotrigine (Lamictal) Tramadol (Ultram) Venlafaxine ER (Effexor)</td>
</tr>
<tr>
<td>Topical</td>
<td>Mechanism of action</td>
<td>Capsaicin (Zostrix) Lidocaine (Lidoderm)</td>
</tr>
<tr>
<td>Other</td>
<td>≥ 1 RCTs in other painful neuropathies or other evidence</td>
<td>Bupropion (Wellbutrin) Citlopiram (Celexa) Methadone (Dolophine) Paroxetine (Paxil) Phenytoin (Dilantin) Topiramate (Topamax)</td>
</tr>
</tbody>
</table>

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### Considerations: First-Tier Agents

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recommended</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma, orthostasis, cardiac or ECG abnormality, hypertension</td>
<td>Any other first-tier agent</td>
<td>TCAs</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Any first-tier agent</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>Any other first-tier agent</td>
<td>Duloxetine, TCAs</td>
</tr>
<tr>
<td>Falls or balance issues</td>
<td>Any other first-tier agent</td>
<td>Pregabalin, TCAs</td>
</tr>
<tr>
<td><strong>Psychiatric comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Duloxetine, TCAs</td>
<td>Oxycodone CR, pregabalin</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Any other first-tier agent</td>
<td>Oxycodone CR</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Duloxetine, pregabalin</td>
<td>TCAs, oxycodone CR</td>
</tr>
</tbody>
</table>

First-tier agents are: duloxetine, oxycodone CR, pregabalin, TCAs

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### Recommendations for Modifying Therapy

- If patients do not respond adequately to first-line treatment or complain of adverse events, it may be necessary to modify their treatment.
  - Change to another first-line agent: use MOA to guide switch
  - Change to a second-line agent: use MOA to guide switch
  - Add a different first- or second-tier agent: use principles of rational polypharmacy (complementary MOA, avoid additive AE, consider possible synergy)

First-tier agents are: duloxetine, oxycodone CR, pregabalin, TCAs

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### Considerations: First-Tier Agents

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recommended</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatic issues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>Any first-line agent</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Second-tier agent, venlafaxine</td>
<td>All first-tier agents</td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>TCAs, generic oxycodone CR</td>
<td>Duloxetine, pregabalin</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Oxycodone CR, pregabalin</td>
<td>Duloxetine, TCAs</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Duloxetine, oxycodone CR</td>
<td>TCAs, pregabalin</td>
</tr>
<tr>
<td>Edema</td>
<td>Any other first-tier agent</td>
<td>Pregabalin</td>
</tr>
</tbody>
</table>

First-tier agents are: duloxetine, oxycodone CR, pregabalin, TCAs

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**Mayo Clin Proc 2006;81(4S)**
### Rationale Polypharmacy for PDN

<table>
<thead>
<tr>
<th>First-tier agent</th>
<th>Add-on therapy</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>α₂δ ligands, opioids, topical agents</td>
<td>Other SNRIs, TCAs, tramadol</td>
</tr>
<tr>
<td>α₂δ ligands</td>
<td>SNRIs, TCAs, opioids, tramadol, opioids</td>
<td>Other α₂δ ligands</td>
</tr>
<tr>
<td>TCAs</td>
<td>α₂δ ligands, opioids, topicals</td>
<td>SNRIs, tramadol</td>
</tr>
<tr>
<td>Opioids</td>
<td>SNRIs, α₂δ ligands, TCAs, opioids, topicals</td>
<td>Other opioids</td>
</tr>
<tr>
<td>Tramadol</td>
<td>α₂δ ligands, opioids, topicals</td>
<td>SNRIs, TCAs</td>
</tr>
<tr>
<td>Topical agents</td>
<td>SNRIs, α₂δ ligands, TCAs, opioids, tramadol, topicals</td>
<td>None</td>
</tr>
</tbody>
</table>

SNRIs – duloxetine, venlafaxine; α₂δ ligands – pregabalin, gabapentin  
TCAs – amitriptyline, desipramine, nortriptyline; opioids – oxycodone, methadone  
Mayo Clin Proc 2006;81(6)

### Audience Response

- MJ is a 74 year old woman with PDN. Her physician prescribed duloxetine (Cymbalta) and her pain improved about 20%. Addition of which of the following agents would be an example of IRRATIONAL polypharmacy?
  - A. despiramine
  - B. gabapentin
  - C. oxycodone CR
  - D. capsaicin