Diagnostic Approach and Management of Painful Diabetic Peripheral Neuropathy

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Disclosure

- No disclosure or conflict of interest
Objectives

▪ To discuss the various forms of diabetic peripheral neuropathy (DPN)

▪ To summarize simple, sensitive and cost-effective diagnostic steps for people with DPN

▪ To provide new evidence-based recommendations for the prevention and management of painful DPN
Case

- 60 year old man with 12 years of type 2 diabetes (HbA1c 8-9%), hypertension, dyslipidemia, CAD and chronic low back pain presenting for a clinic visit with burning pain in both feet, worse at night.

- Medications: Metformin 2000 mg/day, lisinopril 40 mg/day, metoprolol 100 mg/day, atorvastatin 80 mg/day, aspirin 81 mg/day, amitriptyline 75 mg/day (recently added by PCP), oxycodone 15 mg q6 hours prn (for back pain)

Lab:
- POC HbA1c 8.2%
- Total cholesterol 190 mg/dL
- LDLc 70 mg/dL
- Triglycerides 256 mg/dL
- HDLc 38 mg/dL

Examination
- BP: 140/85 mmHg
- BMI: 35
- Central adiposity
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Classification of Diabetic Neuropathies

**Diabetic Neuropathy**

- **Diffuse**
  - Distal Symmetric Polyneuropathy (DSPN)
  - Small Fiber
    - Nociception, Protective Sensation
  - Large Fiber
    - Pressure, Balance
  - Mixed Small & Large Fiber (Most Common)

- **Mononeuropathy**

- **Radiculopathy**

- **Autonomic Neuropathy**

**Nondiabetic Neuropathies common in Diabetes**
- Pressure palsies
- Chronic inflammatory demyelinating polyneuropathy
- Radiculoplexus neuropathy
- Acute painful small-fiber neuropathies (treatment induced)

Adapted from Pop-Busui, Boulton, et al, Diabetes Care 2017;40:136-154
DPN: Involved Nerve Fibers and Pattern of Loss

Large myelinated fiber
Pressure, Balance

Small myelinated fiber

Unmyelinated fibers
Nociception, Protective Sensations
DPN: Involved Nerve Fibers and Pattern of Loss

- Large myelinated fiber: Pressure, Balance
- Small myelinated fiber
- Unmyelinated fibers: Nociception, Protective Sensations
Objectives

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Evaluation of Small Myelinated Fibers in Clinical Care

Nerve Function
- Nociception (pain and temperature)
- Protective sensations

History
- Burning
- Lancinating
- Electric shocks
- Stabbing
- Hyperalgesia
- Allodynia

Exam
- Thermal discrimination (hot/cold)
- Pinprick sensation

Evaluation of Large Myelinated Fibers in Clinical Care

Nerve Function
- Pressure
- Balance

History
- Numbness
- Tingling
- Poor balance

Exam
- Vibration perception
- Proprioception
- Ankle reflexes
- 10 gm monofilament

Diagnosis of DPN
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>15 items</th>
<th>6 item symptom score</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exam</td>
<td>Inspection Vibration testing Ankle Reflexes</td>
<td>Reflex score (knee, ankle) Sensory test score (pinprick, temperature, light touch, vibration and position sense)</td>
<td>Sensation (vibration, temperature, pin-prick) Ankle Reflexes</td>
</tr>
<tr>
<td>DPN +</td>
<td>≥4 points for questionnaire ≥2 for exam</td>
<td>6-8: Mild neuropathy 9-11: Mod neuropathy ≥12: Severe neuropathy</td>
<td>0-2: Mild neuropathy 6-8: Mod neuropathy 9-10: Severe</td>
</tr>
</tbody>
</table>

DPN Screening

Type 1 diabetes

Begin: After 5 years of diagnosis

Frequency: Annually

Type 2 diabetes

Begin: At the time of diagnosis

Frequency: Annually

*Feet at high risk for ulceration should be inspected at every visit – includes known neuropathy, prior ulceration or amputation

ADA Standards of Care: 2022
DPN Screening

Screening: 2 or more of the following
- Temperature, Vibration, Pinprick, light touch or reflexes
- Distal to Proximal
- Symmetric
Prevalence of DPN in Diabetes Mellitus

Up to 35% after >25 years of diabetes

Type 1 Diabetes


Up to 50% after 10 years of diabetes

Type 2 Diabetes

DPN prevalence in youth

Diabetes in Youth Cohort (SEARCH) study
~2,000 youth with T1D and T2D

- **Type 1 Diabetes**
  - SEARCH: Prevalence of 7% after ~9 years of diabetes

- **Type 2 Diabetes**
  - SEARCH: 22% prevalence after ~9 years of diabetes.

Jaiswal, Busui et al; Diabetes Care Volume 40, September 2017
Painful DPN

PREVALENCE

Up to 25%

RISK FACTORS

- Female
- Age
- Duration of diabetes
- Obesity

CLINICAL IMPLICATIONS

- Insomnia
- Mood disorders
- Poor quality of life

DPN and Diabetic Foot Ulcers

Annual incidence of foot ulcers is 2-6%
Lifetime risk of foot ulcers is 15-34%

American Diabetes Association “Diagnosis and Management of Diabetic Foot Complications” 2018
5 year mortality % rivals that of cancer

DPN and Impaired Functionality

Impaired control of the accelerator pedal during driving activities

5-fold increased risk of falling

15-fold increased risk

Increased mortality and decreased quality-of-life

Brown SJ, Boulton AJM et al; Diabetes Care 2014;38:1116-22.
Perazzolo D, Boulton AJM et al; Diabetic Medicine 2019; 00:1-8.
Painful DPN is Associated with Increased Mood Symptoms

Table 4
Scores on QOL and Related Measures by BPI-DPN Average Pain Severity

<table>
<thead>
<tr>
<th>Subject Scores</th>
<th>BPI-DPN Average Pain Severity</th>
<th>ANOVA F  P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norm-based SF-12v2 scale scores, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>36.1 (11.9)</td>
<td>9.8928, 0.0001</td>
</tr>
<tr>
<td>Role physical</td>
<td>39.1 (10.9)</td>
<td>10.5730, 0.0000</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>43.4 (10.6)</td>
<td>37.5740, 0.0000</td>
</tr>
<tr>
<td>General health</td>
<td>38.7 (11.8)</td>
<td>14.0057, 0.0000</td>
</tr>
<tr>
<td>Vitality</td>
<td>43.9 (11.1)</td>
<td>5.1251, 0.0066</td>
</tr>
<tr>
<td>Social functioning</td>
<td>44.1 (12.1)</td>
<td>16.8391, 0.0000</td>
</tr>
<tr>
<td>Role emotional</td>
<td>43.0 (12.8)</td>
<td>12.7136, 0.0000</td>
</tr>
<tr>
<td>Mental health</td>
<td>46.7 (12.2)</td>
<td>7.0033, 0.0011</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>37.5 (9.8)</td>
<td>20.0572, 0.0000</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>47.8 (12.7)</td>
<td>9.4991, 0.0001</td>
</tr>
<tr>
<td>HADS, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score</td>
<td>6.7 (4.5)</td>
<td>16.8033, 0.0000</td>
</tr>
<tr>
<td>Depression score</td>
<td>6.1 (4.2)</td>
<td>17.4129, 0.0000</td>
</tr>
<tr>
<td>EQ-5D, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D utility scores</td>
<td>0.7 (0.2)</td>
<td>44.7734, 0.0000</td>
</tr>
<tr>
<td>Current health, mean (SD)</td>
<td>63.8 (19.5)</td>
<td>6.2107, 0.0024</td>
</tr>
</tbody>
</table>

Total n’s for individual rows range from 238–254 due to missing values.

<sup>a</sup>P < 0.01 for all pair-wise comparisons, except P < 0.05 for the comparisons of current health scores for the mild vs. moderate and severe pain groups; and P = 0.09 for the comparison of current health scores for the moderate vs. severe pain group.

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Pathogenesis of DPN

Hyperglycemia

DNA Damage
ER Stress
Mitochondrial Dysfunction
Cellular Injury and Irreversible Damage

Dyslipidemia
↑ Triglycerides
↑ LDL
↓ HDL
↑ FFA

Insulin resistance
Insulin + C-peptide

Type 1
Type 2
Both

Electron transport overload
Oxysterols
PI3-K
Akt
Insulin signaling

Glucose
Glycolysis
Protein Oxidation
Lipid Oxidation

FFAs
Insulin

ROS
RNS

DCCT RESULTS: The Good News


Glucose Control and Neuropathy

Rate/100 pt-yrs.
100 90 80 70 60 50 40 30

INTENSIVE
CONVENTIONAL

RETINOPATHY
NEPHROPATHY
DPN and CAN
Challenge in EDIC Study: Glucose Control is Difficult to Maintain

DCCT
Intervention
1983-93

Conventional
mean HbA1c 8.0%

Intensive
mean HbA1c 7.9%

EDIC
Observation
1994-present

DCCT
Training

Conventional

Intensive
## Glycemic Control: Lessons learned from DCCT/EDIC for Type 1 Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>DCCT Baseline %</th>
<th>DCCT Closeout %</th>
<th>EDIC Year 13/14 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical neuropathy</td>
<td>INT</td>
<td>10</td>
<td>15 **</td>
<td>34 *</td>
</tr>
<tr>
<td></td>
<td>CONV</td>
<td>8</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>Abnormal NCS</td>
<td>INT</td>
<td>31</td>
<td>30% Reduction</td>
<td>55 **</td>
</tr>
<tr>
<td></td>
<td>CONV</td>
<td>34</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Confirmed clinical neuropathy</td>
<td>INT</td>
<td>7</td>
<td>9 **</td>
<td>26 *</td>
</tr>
<tr>
<td></td>
<td>CONV</td>
<td>5</td>
<td>16</td>
<td>34</td>
</tr>
</tbody>
</table>
Glucose Control and Neuropathy

Type 1 Diabetes
- Observational Studies
  - Exposure precedes Disease
  - Higher Exposure - Higher Rate of Disease
- Randomized Control Trials
  - Reduced Exposure - Reduce Subsequent Disease
  - DSP ↓ Yes
  - CAN ↓ Yes

Type 2 Diabetes
- Observational Studies
  - Exposure precedes Disease
  - Higher Exposure - Higher Rate of Disease
- Randomized Control Trials
  - Reduced Exposure - Reduce Subsequent Disease
  - DSP ↓ Yes
  - CAN ↓ Yes

Strength, Consistency, Specificity of Evidence

Exercise and DPN

*IENFD = intraepidermal nerve fiber density


Regeneration of nerves
Flow mediated dilation (FMD) response in SFA using Color Doppler Ultrasonography

Fig. 2. Hyperemic dilation of superficial femoral artery in the experimental and control groups at baseline and following 12-week.

Michigan Diabetic Neuropathy Score (MDNS)

Vascular function and neuropathic symptoms
Multifactorial Intervention and Neuropathy


RR 0.44 (0.25-0.77)
P=0.004
Low-grade inflammation and diabetic neuropathy

Dillon, Ang, Busui: Spectrum of Diabetic Neuropathy: New Insights in Diagnosis and Treatment, Annual Review of Medicine April 2023 In press
# Management of Painful DPN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose</th>
<th>Number Needed to Treat*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregabalin</strong></td>
<td>Anticonvulsant</td>
<td>25-75 mg, 1-3x daily</td>
<td>300-600 mg/day</td>
</tr>
<tr>
<td><strong>Duloxetine</strong></td>
<td>Antidepressant</td>
<td>20-30 mg/day</td>
<td>60-120 mg/day</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>Anticonvulsant</td>
<td>100-300 mg, 1-3x daily</td>
<td>1800-3600 mg/day</td>
</tr>
<tr>
<td><strong>Amitryptyline/Tricyclics</strong></td>
<td>Antidepressant</td>
<td>10-25 mg daily</td>
<td>25-100 mg/day</td>
</tr>
<tr>
<td><strong>Capsaicin 8%</strong></td>
<td>Topical</td>
<td>Apply on mapped painful areas of the feet, up to a total combined surface area of 1,120 cm² for both feet for 30 minutes</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*Based on 30-50% improvement in symptoms

**FDA approved for painful DPN treatment
Combination Therapy: COMBO-DN Study

- RCT comparing high dose monotherapy with duloxetine or pregabalin compared to combination therapy

- First phase: 8 weeks of low-dose monotherapy

- Second phase: Non-responders (<30% improvement in pain symptoms) from phase 1 given high dose monotherapy vs combination therapy

Combination Therapy: OPTION-DM

Multicenter, randomized, crossover trial
N=130 started a first pathway (amitriptyline supplemented with pregabalin; A-P)
N= 97 started a second pathway (pregabalin supplemented with amitriptyline; P-A)
N= 84 started a third pathway (duloxetine supplemented with pregabalin; D-P)

Mean daily pain intensity of the treatment pathways comparing participants who started combination therapy with those remaining on monotherapy.

Tesfaye et al: Lancet Vol 400 August 27, 2022
• Up to 28-33% of patients receive an opioid as a first-line agent for painful DSPN.

• Opioids are associated with poor functional status, increased risk for dependency and opioid overdoses.

• One FDA approved opioid: Tapentadol

Is pain due to DPN confirmed?

Yes
Assess comorbidities, potential for AEs, drug interactions, costs to select initial therapy from the 3 choices below

* Voltage gated α2-δ ligand (pregabalin, gabapentin)
** Serotonin-norepinephrine reuptake inhibitor (duloxetine, venlafaxine)
Secondary amine Tricyclic Antidepressant (nortriptiline, Desipramine)

Capsaicin 8% patch

NO OPIOIDS!
No clinically meaningful effect

Switch to another agent from above
Try combining agents from above

No clinically meaningful effect/ Not tolerated
Refer to Pain Clinic

Adapted from Pop-Busui, Boulton, et al, Diabetes Care 2017, 40: 136-54
Case

- 60 year old man with 12 years of type 2 diabetes (HbA1c 8-9%), hypertension, dyslipidemia, CAD and chronic low back pain presenting for a clinic visit with burning pain in both feet, worse at night.

- Medications: Metformin 2000 mg/day, lisinopril 40 mg/day, metoprolol 100 mg/day, atorvastatin 80 mg/day, aspirin 81 mg/day, amitriptyline 75 mg/day, oxycodone 15 mg q6 hours prn (for back pain)

Examination
BP: 140/85 mmHg
BMI: 35
Central adiposity

Laboratory:
POC HbA1c 8.2%
Total cholesterol 190 mg/dL
LDLc 70 mg/dL
Triglycerides 256 mg/dL
HDLc 38 mg/dL
Q.1) What should be the next diagnostic steps?

A. Refer to neurology and EMG testing.
B. Perform a focused neurological exam in the office and test for vibration and pinprick touch sensation in the office.
C. Assess light touch sensation in the office.
D. Check Vitamin B12 and serum immunoelectrophoresis.
Diagnosis of DPN in Clinical Care
Q.1) What should be the next diagnostic steps?

A. Refer to neurology and EMG testing.
B. Perform a focused neurological exam in the office and test for vibration and pinprick touch sensation in the office.
C. Assess light touch sensation in the office.
D. Check Vitamin B12 and serum immunoelectrophoresis.

Correct Answers: B, D
DPN Mimics

**METABOLIC DISEASE**
- Thyroid
- Renal

**SYSTEMIC DISEASE**
- Vasculitis
- Paraproteinemia
- Amyloidosis

**INFECTIOUS**
- HIV
- Hepatitis B
- Lyme disease

**INFLAMMATORY**
- Chronic inflammatory demyelinating polyradiculoneuropathy

**NUTRITIONAL**
- Vitamin B12 deficiency
- Pyridoxine
- Thiamine
- Tocopherol

**INDUSTRIAL AGENTS**
- Acrylamide
- Organophosphorous agents

**DRUGS**
- Alcohol
- Amiodarone
- Chemotherapy

**HEAVY METALS**
- Arsenic
- Mercury

**HEREDITARY**

Q.2) How would you manage pain in this patient?

A. Start amitriptyline 50 mg at night
B. Prescribe pregabalin 75 mg twice/day and titrate dose to 300 mg/day
C. Recommend tapentadol extended release 50 mg twice a day
D. Stop oxycodone
Q.2) How would you manage pain in this patient?

A. Start amitriptyline 50 mg at night
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C. Recommend tapentadol extended release 50 mg twice a day
D. Stop oxycodone

Correct Answer: B and D
Take Home Messages

• DPN is a prevalent complication of both type 1 and type 2 diabetes.

• Has important clinical consequences: severe pain, impaired function, low quality of life, depression and anxiety, increased mortality, and amputation risk.

• It can be easily diagnosed using history, targeted physical examination and simple, readily available instruments.
  – Sophisticated techniques and referrals to neurology are rarely needed, unless symptoms and signs are atypical.

• Pain management should follow evidence and avoid narcotics.
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Thank you