Diabetic neuropathies (DNs) are the most prevalent chronic complications of diabetes, with multiple manifestations, consistent risk factors, and complex pathogenetic mechanisms. There are multiple types of DN and each presents with a unique array of symptoms and clinical signs, but distal symmetrical polyneuropathy is the most prevalent form. Screening for symptoms and signs of DN is critical in clinical practice to enable early intervention and prevent late complications. Neuropathic pain may be the first symptom that prompts patients to seek medical care and is present in up to 25% of individuals with DN. Characteristically, the pain is burning, lancinating, tingling, or shooting (electric shock-like), with paresthesias, occurring in varying combinations, and is typically worse at night. Despite the recent major advances in elucidating the pathogenesis of diabetic neuropathy, there remains a lack of treatment options that effectively target the natural history of DNs. However, pharmacological management for pain using drugs of different classes is available.

Several recent guidelines and systematic reviews have addressed the evidence base for the treatment of neuropathic pain and agents with evidence of effectiveness for DN pain will be discussed.
Case 1

- 55 yo Hispanic female presents to the office for progressive severe, shooting pain from both feet up to her ankles, worse at night
- Claims her skin is “on fire,” and she cannot tolerate even the touch of clothing or bed sheet
- Reports no other known medical problems and was not taking any medications

Mrs. R.S.’s Initial Physical Examination

- Height: 5 ft 3 in; Weight: 182 lbs
- BP: 145/90 mm Hg; Pulse: 72 beats/min
- Abdominal obesity
- Unremarkable Head/Neck, Lungs, Cardiovascular, extremities

Mrs. R.S.’s Test Results

- Comprehensive metabolic panel, TSH, CBC, folate, protein electrophoresis: WNL
- Urine: Negative for protein
  - Random glucose: 138 mg/dL
  - HbA1c: 6.4%

Mrs. R.S.: Test Results

- Fasting lipid profile:
  - Total cholesterol: 230 mg/dL
  - LDL-C: 140 mg/dL
  - HDL-C: 40 mg/dL
  - Triglycerides: 256 mg/dL
- Oral Glucose Tolerance Test
  - Fasting blood glucose (FBG): 118 mg/dL
  - 2-h post glucose load: 194 mg/dL
The Peripheral Nervous System is Complex

<table>
<thead>
<tr>
<th>Large Myelinated Fibers</th>
<th>Small Myelinated &amp; Unmyelinated Fibers</th>
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<tbody>
<tr>
<td>Function</td>
<td>Pressure, balance</td>
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<tr>
<td>Nociception: protective sensation</td>
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<tr>
<td>Symptom</td>
<td>Numbness</td>
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<tr>
<td>Tingling</td>
<td>Pain</td>
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<tr>
<td>Poor balance</td>
<td>Burning, electric shocks, stabbing pain</td>
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<tr>
<td>Exam</td>
<td>Reflexes, proprioception</td>
</tr>
<tr>
<td>Vibration, heat</td>
<td>Thermal, pin-prick sensation</td>
</tr>
<tr>
<td>Diagnostics Test</td>
<td>NCV Testing (median, sural, peroneal nerves)</td>
</tr>
<tr>
<td>For research only</td>
<td>Historically “invisible” Skin Biopsy for IENFD, Corneal confocal microscopy, QST (thermal, pain), Sudomotor function (Neuropad, Sudoscan)</td>
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</tbody>
</table>

Diabetic Peripheral Neuropathy

Large myelinated fiber Small myelinated fiber Unmyelinated fibers

1. Appearance
   - Normal? Yes (0)
   - If no: Deformities? Yes (1)
   - Dry Skin/Callus? Yes (1)
   - Infection? Yes (1)
   - Fissure? Yes (1)
2. Ulceration
   - Absent (0)
   - Present (1)
3. Vibration (c128hz)
   - Present (0)
   - Reduced (0.5)
   - Absent (1)
4. Ankle Reflex
   - Present (0)
   - Present with reinforcement (0.5)
   - Absent (1)

DPN Diagnosis Michigan Neuropathy Screening Instrument

DPN is present if a score >2

Mrs. R.S.’s Examination

Neurological
- Intact light touch and vibration
- Symmetrical impairment in pinprick and in cold temperature discrimination up to ankle

Claims her skin is “on fire,” and she cannot tolerate even the touch of clothing or bed sheet

Diabetic Neuropathy Pain

Neuropathic pain

Hyperalgesia: exaggerated response to painful stimuli

Allogdynia: pain evoked by contact, e.g., with socks, shoes, and bedclothes.

Document that is due to DN!
Diabetic Neuropathy Pain

**GRADING**

- The modified Likert scale (0=no pain; 10=worst possible pain)
- The visual analogue scale (VAS)

McGill Pain Scale Short Form-2,
The Neuropathic Pain Symptom Inventory (NPSI),
The Neuropathic Pain Scale
The Neuropathy Total Symptom Score-6 (NTSS-6)

**Nociception leads to pain; How much pain is experienced depends upon**

- **Context**
  - pain beliefs
  - expectation
  - placebo

- **Cognitive Set**
  - hyper vigilance
  - attention
  - distraction
  - catastrophising

- **Injury**
  - peripheral & central
  - sensitisation

- **Mood**
  - depression
  - catastrophising
  - anxiety

- **Chemical & Structure**
  - neurodegeneration
  - metabolic eg opioidergic, dopaminergic
  - maladaptive plasticity

**Consequences of Pain**

Severe pain, polypharmacy
Physical disabilities
Low quality of life

**How to Treat Neuropathic Pain in Diabetes?**

**Pain Diary: A 30% Reduction is a Clinically Important Improvement**

PGIC=Patient’s Global Impression of Change

**Management of Painful DPN**

- Pharmacotherapy
- Neurostimulatory
- Interventional Regional Anesthesia
- Physical Rehabilitation
- Psychological
- Lifestyle
Treating Neuropathic Pain

Only 2 medications, pregabalin and duloxetine, have received regulatory approval for the treatment of neuropathic pain in diabetes by the United States Federal Drug Agency (FDA), Health Canada, and the European Medicines Agency (EMA).

The opioid, tapentadol, has regulatory approval in the United States and Canada.

Evidence: Pharmacotherapy For Neuropathic Pain - Number Needed to Treat

Publication bias:
Studies published in peer-reviewed journals reporting greater effects than did the unpublished studies

Finnerup et al., Lancet Neurology, 2015, 14: 162-73

Drug Class | Agent | Dose | NNT Range | Common AEs | Major AEs
--- | --- | --- | --- | --- | ---
Anticonvulsants
Pregabalin
Gabapentin

Initial | Effective | 30-50% Improvement | 3.3-7.7

Common AEs
- Somnolence
- Dizziness
- Ataxia
- Fatigue

Major AEs
- Stevens-Johnson syndrome
- Suicidal thoughts and behaviour
- Suicides after rapid discontinuation

Requires gradual titration to the clinically effective dose.

Drug Class | Agent | Dose | NNT Range | Common AEs | Major AEs
--- | --- | --- | --- | --- | ---
Antidepressants - SNRI
Duloxetine

Initial | Effective | 30-50% Improvement | 3.8-11

Common AEs
- Nausea
- Somnolence
- Dizziness
- Constipation
- Dyspepsia
- Dizziness
- Headache
- Accessory
- Peptic
- Dipsiness
- Dizziness
- Fatigue
- Decreased libido

Major AEs
- Stevens-Johnson syndrome
- Neutropenia
- Hypertension
- Hypotensive crisis
- GI hemorrhage
- Delirium
- SIADH
- Amyotrophy
- Gliosis
- Suicidal thoughts Shift to mania
- Suicides
<table>
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<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Initial Dose</th>
<th>Effective Dose</th>
<th>NNT Range</th>
<th>Common AEs</th>
<th>Major AEs</th>
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<tbody>
<tr>
<td>Antidepressants - SNRI</td>
<td>Venlafaxine</td>
<td>75-225 mg/day</td>
<td>5.2-8.4</td>
<td>Nausea</td>
<td>Somnolence</td>
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<td>Decreased Libido</td>
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**Initial Effective**

**30-50% improvement**

**Common AEs Major AEs**

**Antidepressants - SNRI**

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<th><strong>Venlafaxine</strong></th>
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<th><strong>Effective Dose</strong></th>
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<th><strong>Major AEs</strong></th>
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<td><strong>Initial</strong> Dose</td>
<td>37.5 mg/day</td>
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<td>5.2-8.4</td>
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**Antidepressants - SNRI**

**Amitriptyline**

- A most recently updated Cochrane Review based on evidence reported that in fact there is no good quality, unbiased evidence for a beneficial effect for amitriptyline.

These facts should be balanced in treatment decision making as only a minority of people will achieve satisfactory pain relief.

There is an increased risk of myocardial ischemia and arrhythmogenesis associated with tricyclic agents.

**Secondary amines - nortriptyline and desipramine.**

- Have a less troublesome side-effect profile
- Effectiveness appeared unrelated to the antidepressant effect
- Their use is preferable, particularly in the elderly and side-effect prone patients.

**Opioid and atypical opioid analgesics**

**Tramadol:**
- low affinity binding to the μ opiate receptor
- inhibits reuptake of norepinephrine and serotonin
- analgesia only partially antagonized by naloxone.

**Tapentadol:**
- centrally-acting analgesic through both μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition.
- Extended-release tapentadol was approved by FDA for the treatment of diabetic neuropathic pain based on data from 2 randomized-withdrawal, placebo-controlled Phase 3 trials.
- Most recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain found the evidence of the effectiveness of tapentadol inconclusive.

**Over the counter agents**

There are multiple over the counter agents (herbal supplements, vitamins, minerals) that are occasionally recommended for neuropathic pain.

Currently, the available evidence is questionable re benefits and given the possibility for harm (associated with lack of consistency in regulation of active substance or the fillers), prescribing these agents in the absence of evidence obtained from properly designed randomized clinical trials is not recommended.
Is pain due to DSPN confirmed?

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

No/Not sure
- Refer to Neurology/Pain Clinic

Voltage gated α2-δ ligand (pregabalin, gabapentin)

Serotonergic/norepinephrine reuptake inhibitor (duloxetine, venlafaxine)

Secondary amine Tricyclic Antidepressant (nortriptiline, Desipramine)

No clinically meaningful effect
- Switch to another agent from above
- Try combining agents from above
- May add tramadol or tapentadol if a/w or fail

No clinically meaningful effect/Not tolerated
- Refer to Pain Clinic

Few Take Home Messages

- DN is a very prevalent diabetes complication
  It may be present at the time of T2D diagnosis and in patients w/impaired glucose tolerance/metabolic syndrome

- It can be easily diagnosed using:
  Appropriate history to unveil specific symptoms
  Targeted physical examination and simple instruments to confirm neuropathy pattern (distal-to-proximal), symmetrical findings, and, if not, predominant sensory over motor deficits

- Sophisticated techniques and referrals to neurology are rarely needed, unless symptoms and signs are atypical.

Few Take Home Messages

- Only 2 medications, pregabalin and duloxetine, have received regulatory approval for the treatment of neuropathic pain in diabetes by the United States Federal Drug Agency (FDA), Health Canada, and the European Medicines Agency (EMA).

- The opioid, tapentadol, has regulatory approval in the United States and Canada, but evidence regarding its effectiveness is inconclusive.

- Despite the demonstrated effectiveness of opioids in the treatment of neuropathic pain, there are ongoing concerns with respect to abuse, addiction, diversion, and other psychosocial issues.

- For these reasons, opioids should not be used before failure of other agents that do not have these associated concerns and referral to a pain clinic should be considered before opioid use.