Small Fiber Neuropathy (SFN)

Ibrahim Alkhodair
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Terminology

• **Polyneuropathy**: a generalized process affecting many peripheral nerves, with the distal nerves usually affected most prominently.

• **Mononeuropathy**: a focal neuropathy affecting one nerve.

• **Peripheral neuropathy**: a less precise and can refer to any disorder of the peripheral nervous system including polyneuropathy, radiculopathies and mononeuropathies.
**Axonal neuropathy:** Usually from systemic disorders (DM, HIV, uremia, critical illness), toxins

**Demyelinating neuropathy:** Usually from autoimmune and hereditary causes

**Axonal vs. Demyelinating lesions**

<table>
<thead>
<tr>
<th></th>
<th>Axonal</th>
<th>Demyelinating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitudes</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Distal latency</td>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>Normal</td>
<td>Slow</td>
</tr>
</tbody>
</table>
Introduction

• **Most** peripheral neuropathies have mixed involvement of small and large fibers.

• **Small fiber neuropathy (SFN)** refers to a group of neuropathies characterized by a selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibers and unmyelinated C-fibers.
Peripheral nerves
## Small Vs Large fiber neuropathy

<table>
<thead>
<tr>
<th>Small fiber neuropathy</th>
<th>Large fiber neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and paresthesia</td>
<td>Impaired vibration</td>
</tr>
<tr>
<td>Autonomic signs and symptoms</td>
<td>Loss of position sense</td>
</tr>
<tr>
<td>Temperature loss</td>
<td>Wasting and weakness of muscles</td>
</tr>
<tr>
<td>No weakness</td>
<td>Loss of deep tendon reflexes</td>
</tr>
<tr>
<td>Normal deep tendon reflexes</td>
<td></td>
</tr>
</tbody>
</table>

**Positive Sx**

**Negative Sx**
Epidemiology

- The only study that addressed the incidence of SFN was performed in The Netherlands in 2013.
- It reported an incidence of 11.73 cases (15.6 male/8.2 female) per 100,000 population per year, with higher rates in those >65 years of age.
- Prevalence was 52.95 cases (60.9 male/45.4 female) per 100,000/year.
SFN - patterns

• **Length – dependent (LD-SFN):**
  - Most common
  - Stocking and glove pattern: starts in feet and moves proximally.
  - Pure SFN – usually confined to feet

• **Non-length-dependent (NLD-SFN):**
  - Functional impairment of individual or multiple nerves or nerve fibers.
  - Variable patchy sensory pattern that can affect different parts of the body, including the face, tongue, scalp, upper limb, and trunk, **before the lower limbs**.
  - Observed in paraneoplastic, immune mediated, and idiopathic cases of SFN.
  - **Burning mouth syndrome:** intraoral burning sensation +/- itching, altered taste sensation. Predominantly affects post menopausal-females.
<table>
<thead>
<tr>
<th></th>
<th>LD-SFN</th>
<th>NLD-SFN</th>
<th>P-value</th>
</tr>
</thead>
</table>
| Symptoms             | From distal to proximal                     | 1. Involving proximal regions of the limbs, face, or trunk.  
2. Onset of symptoms in the face, scalp, mouth, tongue, trunk, hands, arms, or proximal legs before the feet.  
3. Pain that begins in proximal and distal regions of the limbs simultaneously. |           |
| Demographics         |                                             |                                           |           |
| Women                | 48%                                         | 73%                                       | <0.001    |
| Age at diagnosis     | 66.0 ± 11.3                                 | 53.5 ± 12.2                               | 0.003     |
| Age at onset         | 63.3 ± 11.9                                 | 50.7 ± 12.9                               | 0.005     |
| Symptoms             |                                             |                                           |           |
| Described as itchy   | 3%                                          | 36%                                       | 0.010     |
| Reported touch alodynia | 27%                                      | 72%                                       | 0.012     |
| Causes/associations  |                                             |                                           |           |
| DM/IGT               | 48% 3.4%                                    | 9% 14.3%                                  | 0.031 0.012 |
| Immunomediates       |                                             |                                           |           |
| conditions           |                                             |                                           |           |
|                      | (lupus, MCTD, RA, psoriasis, sarcoidosis, Sjögren syndrome, scleroderma) |                                           |           |
| Prognosis            | Satisfactory response with 1 or 2 non-narcotic analgesics. | Limited response to immune therapies; often refractory to aggressive symptomatic pain management with 3 or 4 moderate- to high-dose narcotics. |           |

*Summarized and significant values taken from earlier studies. DM, diabetes mellitus; IGT, impaired glucose tolerance; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis.*
Box 1 | Symptoms of small-fibre neuropathy

For the diagnosis of small-fibre neuropathy, at least two of the following symptoms, not otherwise explained, are required.

**Sensory**
- Pain (burning, shooting, prickling or itching)
- Paraesthesias
- Allodynia
- Thermal sensory loss
- Pinprick loss
- Sheet or sock intolerance
- Restless legs syndrome

**Autonomic**
- Sicca syndrome
- Accommodation problems
- Hyperhidrosis or hypohydrosis
- Micturation disturbances
- Impotence and/or diminished ejaculation or lubrication
- Bowel disturbances (constipation, diarrhoea, irritability, gastroparesis, cramps)
- Hot flushes
- Orthostatic dizziness
- Cardiac palpitations
SFN – Clinical features

• **Pain and paresthesia:**
  1. burning, prickling, aching, electric-like, or itching sensation, restless leg.
  2. Usually worse at night.
  However, it can be **painless**

• **Autonomic symptoms:** dry eyes, dry mouth, palpitations, orthostatic hypotension, constipation, urinary retention, sexual dysfunction, sweating abnormalities, and skin discoloration.
SFN – Examination

- Reduced or absent sensitivity to cold, heat, and noxious mechanical stimuli.
- Sensory loss can occasionally be masked by simultaneous hyperalgesia and allodynia in the affected area.
- Patients might complain of abnormal altered sensations to thermal stimuli (e.g. cold stimuli might be perceived as heat).
- Associated skin changes in affected areas may include dry, cracked, or shiny skin, with decreased moisture on the surface of these affected areas as well.

- **Motor strength, proprioception, vibration, and deep tendon reflexes are usually preserved**
Difficulties when dealing with SFN

1- The course of neuropathy can progress over time from pure SFN to mixed

2- No criteria available for NLD-SFN

3- Most diagnostic tests are time-consuming, require specific expertise, and not readily available.

4- SFN can occur secondary to multiple conditions (e.g. fibromyalgia, motor neuron diseases, Ehlers-Danlos syndrome, Parkinson disease ...
Etiologies

Primary:
• Idiopathic (30-50%)
  ▶ Idiopathic small fiber neuropathy
  ▶ Burning mouth syndrome

• Hereditary/genetic (suspect especially if young age and/or +ve family history)
  ▶ Hereditary sensory and autonomic neuropathies
  ▶ $\text{Na}_\text{v}1.7$ mutations
  ▶ $\text{Na}_\text{v}1.8$ mutations
  ▶ Familial amyloid polyneuropathy
  ▶ Fabry's disease
  ▶ Tangier's disease: decreased/absent HDL $\rightarrow$ accumulation of foamy macrophages $\rightarrow$ HSM, accelerated atherosclerosis, neuropathy in 50%.
Etiologies

**Voltage-gated sodium channelopathies:**

- A gain-of-function mutations in *SCN9A*, *SCN10A*, *SCN11A*, encoding Nav1.7, Nav1.8, and Nav1.9 α-subunit isoforms of the voltage-gated sodium channels that are preferentially expressed in small-diameter dorsal root ganglion (DRG) neurons, trigeminal neurons.

- The voltage-gated sodium ion channel Nav1.7 is expressed selectively in sensory and autonomic neurons.

- Inactivating mutations in *SCN9A*, which encodes Nav1.7, result in congenital insensitivity to pain, whereas gain-of-function mutations in this gene produce distinct pain syndromes such as inherited erythromelalgia, paroxysmal extreme pain disorder, and **small-fiber neuropathy**.

- Variants of genes coding for the voltage-gated sodium channels Nav1.8 (SCN10A) and Nav1.9 (SCN11A) lead to small-fiber neuropathy and congenital insensitivity to pain, respectively.
Hereditary sensory and autonomic neuropathies

- **Type 1**: Most common, autosomal dominant, usually in adulthood.

- **Type 2**: Prominent sensory abnormalities, recurrent digital infections.

- **Type III (familial dysautonomia)**: Characteristic smooth tongue, it is predominantly seen in Ashkenazi Jewish infants.

- **Type IV**: Severe anhidrosis, and insensitivity to pain.

- **Type V**: Affected deep pain perception, and thus, severe injuries such as bone fractures and joint injuries.

<table>
<thead>
<tr>
<th>HSAN</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
<th>Type V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of clinical manifestation</td>
<td>Adulthood (20–40th decade)</td>
<td>Infancy, early childhood</td>
<td>Birth</td>
<td>Infancy, early childhood</td>
<td>Infancy</td>
</tr>
<tr>
<td>Most prominent nerve fiber reduction (sural nerve biopsy)</td>
<td>Small fibers</td>
<td>Myelinated fibers</td>
<td>Small fibers, and significant loss of sympathetic neurons</td>
<td>Absence of unmyelinated fibers, and loss of sympathetic fibers</td>
<td>Selective decrease of small myelinated fibers</td>
</tr>
<tr>
<td>Prominent clinical neurological features (history &amp; clinical findings)</td>
<td>Ulcers, mutilations of lower limbs, lancinating pain, muscle weakness, stepwise gait, etc.</td>
<td>Ulcers, mutilations of hands and feet, Charcot joints, fractures, impaired sensory qualities</td>
<td>Ashkenazi Jews, ancestry, diminished deep tendon reflexes, lack of overflow bladders, absence of lingual fungiform papillae, no axon flare response to intrathecal lidocaine, preserved visceral pain</td>
<td>Unnoticed injuries &amp; fractures, episodes of fever with high environmental temperature, cory, hyperkeratotic skin, ulcers, mutilations, Charcot joints, no visceral pain</td>
<td>Repeated unnoticed injuries &amp; fractures, no pain perception</td>
</tr>
<tr>
<td>Quantitative sensory testing of thermal (Aβ- and C-fibers) and vibratory (Aβ-fibers) perception</td>
<td>Abnormal warm, cold, heat pain thresholds</td>
<td>Abnormal vibratory thresholds</td>
<td>Highly abnormal warm, cold, heat pain thresholds</td>
<td>Abnormal thermal thresholds, absent pain perception</td>
<td>Absent heat pain perception</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td>Low normal or slightly reduced motor &amp; sensory conduction velocities</td>
<td>Highly abnormal sensory nerve conduction (absent potential), Low normal motor nerve conduction velocities</td>
<td>“Second” motor compound action potential</td>
<td>May be abnormal (no discomfort with high intensity stimulation)</td>
<td>May be normal</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Hypo- or anhidrosis in distal lower limbs</td>
<td>Episodic hyperhidrosis, anorexia, fever, tense pupils, lacrimation, and tachycardia, and gastrointestinal dysmotility</td>
<td>Orthostatic hypotension, autonomic crises with vomiting, hyperhidrosis, episodic hypertension</td>
<td>Severe anhidrosis</td>
<td>“mutilating” of skin, hyperhidrosis</td>
</tr>
</tbody>
</table>
A. Normal tongue with fungiform papillae present on the tip. B. Dysautonomic tongue. Note the absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue.
Etiologies

Secondary:

- **Diabetes** is the most common known cause
  - Accounts for around 33% of all SFN cases.
  - Might develop insidiously or acutely, as with treatment-induced neuropathy (AKA. Insulin neuritis) caused by fast glycemic control.
### Panel 2: Causes of small fibre neuropathy

#### Metabolic causes
- Diabetes, impaired glucose tolerance, and rapid glycaemic control in the setting of chronic hyperglycaemia (treatment-induced neuropathy of diabetes)
- Hypothyroidism
- Hypertriglyceridaemia
- Uraemia

#### Neurotoxic exposure or vitamin intoxication
- Alcohol
- Antiretroviral agents
- Chemotherapeutic agents
- Organic solvents
- Pyridoxine B6 intoxication
- Statins
- Anecdotal cases: antiarrhythmic drugs (flecainide), antibiotics (metronidazole, nitrofurantoin, linezolid, ciprofloxacin), ingestion of *Clostridium botulinum* toxin, heavy metals (thallium, lead), and tumour necrosis factor α inhibitors

#### Infections
- Hepatitis C virus
- HIV
- Influenza
- Leprosy
- Severe sepsis, septic shock, and critical illness
- Anecdotal cases: Epstein-Barr virus, herpes simplex infection, mycoplasma pneumonia, rubella, syphilis, vaccination for rabies, varicella or Lyme disease, and hepatitis B virus

### Immunological causes
- Autoimmune autonomic ganglionopathy
- Coeliac disease
- Guillain-Barré syndrome, monodonal gammopathies, and primary amyloidosis (immunoglobulin light chain associated)
- Paraneoplastic syndrome
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Vasculitis

### Hereditary causes
- Familial amyloid polyneuropathy (transthyretin amyloidosis)
- Hereditary sensory and autonomic neuropathies
- Fabry disease
- Mutations in COL6A5 and genes encoding voltage-gated sodium channels
- Pompe’s disease

### Idiopathic small fibre neuropathy
Differential Diagnoses

• Complex regional pain syndrome
• Raynaud phenomenon
• Peripheral vascular disease
• Compressive mononeuropathy
• Porphyrias
• Radiculopathy
• Mononeuritis multiplex
Clinical assessment tools

- **Questionnaires**
  - The Small Fiber Neuropathy and Symptoms Inventory Questionnaire: includes 13 items. Each item has four response options: 0=never, 1=sometimes, 2=often, and 3=always.
  - The Autonomic Symptom Profile and the Composite Autonomic Symptom Score-31 (COMPASS-31): developed specifically for autonomic dysfunctions.

- **Examination tools:** The diagnostic accuracy of clinical examination in pure SFN was reported to be 55%
  - Utah Early Neuropathy Scale (UENS): emphasizes the severity and spatial distribution of pin (sharp) sensory loss in the feet and legs.
  - The composite autonomic scoring scale (CASS): includes measurements of orthostatic blood pressure, the quantitative sudomotor axon reflex test, heart rate response to tilt, heart rate variability with deep breathing, and changes in blood pressure with the Valsalva maneuver.
  - Thermoregulatory sweat test
Figure 1. Performing the Utah Early Neuropathy Scale (UENS) examination. The UENS requires a number 2 (1½ inch) safety pin and a 128 Hz tuning fork. Pin sensation is tested by first reviewing normal sharp sensation to pin on an unaffected portion of the skin. Once this is established, touch the dorsal surface of the foot and leg with the pin, working centripetally from the great toe in 1–2 cm increments while asking the subject to respond when they first feel “any sharpness,” and again more proximally when the pin feels “as sharp as they would expect.” Repeat to firmly establish these levels. On each side, 2 points are scored for each region in which the patient fails to feel any sharpness. One additional point is scored for each additional region in which the pin feels less sharp than expected. Only distal sensory loss is scored. So, for instance, a person who reported absent pin sensation to the mid foot dorsum (4 points) and reduced sensation to the low ankle (1 point) bilaterally would score a total of 10 points for this portion of the UENS. Vibration is tested by first acquainting the subject with vibration (as opposed to pressure) sensation, then holding the maximally vibrated tuning fork to the dorsum of the great toe at the distal interphalangeal joint. Extinction of vibration in less than 10 s is considered “diminished,” while “absent” requires that the patient cannot detect the maximally vibrating tuning fork at the toe. The motor examination is limited to great toe dorsiflexion. Other aspects are as typically performed in neurological examination.
Thermoregulatory sweat testing (TSI)
Neurophysiological and pathological techniques

- Nerve biopsy
- Skin biopsy
- Quantitative sensory testing
- Quantitative sudomotor axon reflex test
- Corneal confocal microscopy
- Microneurography
- Electrical-evoked potentials
- Laser-evoked potentials
- Contact heat-evoked potentials
Quantitative sensory testing (QST)

• QST is a non-invasive method that can evaluate both gain and loss of sensory function and can be used to assess the functional impairment of sensory nerve fibers.

• QST is a psychophysical method used to quantify somatosensory function.

• It is based on measurements of responses to calibrated, graded innocuous or noxious stimuli (generally mechanical or thermal).

• Limitations:
  • (1) QST is a psychophysical test and is thus open to bias.
  • (2) Abnormal results do not have a localizing value in terms of the identification of peripheral versus central lesions.
  • (3) It is time-consuming and only available at specialized centers.
Nerve conduction studies

• Usually normal in SFN.
• Done to exclude large fiber involvement.
• However, the involvement of large fibers does not exclude SFN, and overlap is common.
Quantitative sudomotor axon reflex test (QSART)

- Assesses the postganglionic sympathetic cholinergic sudomotor function in the extremities.
- Acetylcholine 10% is iontophoresed into the skin to stimulate unmyelinated C-fibers. And sweating is measured and quantified by a sudorometer.
- Can provide early diagnosis of sudomotor dysfunction and can be used to monitor disease progression or recovery.
Skin biopsy

• Highest diagnostic accuracy, Considered to be the Gold standard.
• The procedure is fast and simple, and the resultant wound heals within a few days.
• Disease progression can therefore be followed up over time by repeated skin biopsies.
• Skin biopsy can also distinguish between somatosensory and autonomic nerve fibers.
Skin biopsy

• Quantitative assessment of intraepidermal nerve fiber density (IENFD)
• Sensitivity and specificity > 90%.
• Other measures:
  - Quantification of axonal swellings: especially in painful neuropathies. Could represent pre-degenerative changes.

• The correlation between IENFD and functional test measures, such as QST, is still unclear, because the quantification of intraepidermal nerve fiber density reveals structural changes, but does not predict the degree of functional changes. The remaining fibers can thus be sensitized, hypofunctional, or normal.

• For example, Patients with erythromelalgia can have altered small fiber function without loss of intraepidermal nerve fibers.
Figure 2: Skin nerve fibres
In a punch skin biopsy, a sample that is usually 3 mm in diameter is removed. After overnight fixation, the sample is frozen and cut into 50-μm thick cryosections (vertically to the direction of the epidermis) and then immunostained with PGP9.5 antibody, to visualise the fibres and estimate their density. (A) Intraepidermal nerve fibres (green arrows) and dermal nerve fibres (white arrows) in a healthy individual. (B) Loss of skin nerve fibres in a patient with painful diabetic neuropathy. (C) Axonal swelling of intraepidermal nerve fibres (white arrow) in a patient with painful diabetic neuropathy.
Nerve biopsy

- Usually of sural nerve
- Virtually never done for pure SFN
- May be used to detect demyelination with associated inflammation in patients with vasculitis or infiltrating diseases as amyloidosis.
Corneal confocal microscopy

• The cornea is innervated by Aδ-fibers and C-fibers that originate from the ophthalmic division of the trigeminal nerve. It is the most densely innervated part of the human body and offers a unique window to small fiber innervation.

• A promising new technique, quantification of small fibers located near the center of the cornea.

• It is non-invasive and fast, and thus might be a useful method to confirm small nerve fiber pathology.

• Multiple parameters measured: nerve fiber length density, nerve fiber branch density, and nerve fiber tortuosity.

• The diagnostic sensitivity and specificity of this technique in diabetic polyneuropathy are 91% and 93%, respectively.

• Can be used to follow up progression and treatment response.
Other tests: research

• Laser-evoked potentials
• Contact heat-evoked potentials
• Microneurography
Biochemical tests

Panel 3: Biochemical markers of small fibre neuropathy

Initial screening in polyneuropathy
Glucose dysmetabolism
- Fasting plasma glucose
- Glycosylated haemoglobin (HbA1c)
- Oral glucose tolerance test in selected cases with normal HbA1c
Renal, thyroid, and liver function
Vitamin deficiency
- Cobalamin
- Homocysteine
- Folate
- Methylmalonic acid
Haematological disease
- Serum protein electrophoresis with immunofixation electrophoresis
Other causes
- Erythrocyte sedimentation rate
- Complete blood count
- IgM, IgA, IgG

Biochemical screening in definite small fibre neuropathy
Acute or subacute development of autonomic dysfunction
- Ganglionic acetylcholine receptor antibodies
- Onconeural antibodies (anti-Hu antibodies, anti-CV2 antibody, voltage-gated calcium channel antibody, voltage-gated potassium channel antibody, Purkinje cell cytoplasmic antibody type 2)
Autoimmune or connective tissue disorder
- Rheumatoid factor
- Antinuclear antibody
- Antineutrophil cytoplasmic antibody screening
- Cryoglobulin
- Interleukin-2 receptor antibody
- Total and free calcium ion
- Serum and urine protein immunofixation electrophoresis
- CSF analysis
Sjogren’s syndrome
- Anti-RO (SSA), anti-La (SSB)
Infection
- HIV tests
- Fluorescent treponemal antibody absorption test
- Hepatitis B and C
- CSF analysis
Diseases of the gut
- Antibodies for coeliac disease (gliadin, transglutaminase, and endomysial)
- Vitamin B and E concentrations
Porphyria
- Blood, urine, and stools for porphyrins
Neurotoxins
- Urine and blood toxicology
Hereditary causes
- Leucocyte α-galactosidase A enzyme activity in men and genetic tests in women for suspected Fabry disease when systemic features of the disease are present
- Genetic testing for SCN9A and SCN10A in patients with suspected Nav1.7α, 1.8α, or 1.9α sodium channelopathies
- Genetic testing for familial transthyretin amyloidosis
Diagnostic criteria for LD-SFN

- From the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB)

1) possible: presence of length-dependent symptoms or clinical signs of small fibre damage, or both)

(2) probable as possible + a normal sural nerve conduction study)

(3) definite: as probable + abnormal QST thresholds at the foot or reduced intraepidermal nerve fiber density at the ankle, or both).
Diagnostic approach

Clinical suspicion
- Symptoms – somatic sensory or autonomic
- Signs - loss of thermal and pinprick sensation

Nerve conduction studies
- abnormal → Large fibre neuropathy
- normal

Quantitative sensory testing
- Skin biopsy
- abnormal → Investigate for causes of small fibre neuropathy (Table 2)
- normal → Investigate for CNS pathology

If no cause found → Idiopathic small fibre neuropathy
Management

- Currently, There are no treatments that can prevent or reverse SFN.

- Treatment of underlying cause
  - Tighter glycemic control in DM
  - Thyroid replacement in hypothyroid...
  - Avoid toxic substances
Treatment for specific conditions

• Enzyme replacement for Fabry Disease
• Some case reports supporting effectiveness of IVIG on sarcoidosis, celiac, Sjogren syndrome.
• Liver transplant for hereditary amyloidosis
• Selective Nav1.7 blockers are currently under development, and might prove effective, especially in patients with SCN9A mutations.
### Symptomatic management

#### Summary of Guidelines

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</thead>
<tbody>
<tr>
<td>Tricyclic Antidepressants</td>
<td>First Line</td>
<td>First Line</td>
<td>First Line for PPN and PHN</td>
<td>First Line</td>
<td>First Line</td>
</tr>
<tr>
<td>SNRIs</td>
<td>First Line</td>
<td>Second Line</td>
<td>First Line for PPN</td>
<td>Third Line</td>
<td>Second Line³</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>First Line</td>
<td>First Line</td>
<td>First Line for PPN and PHN</td>
<td>Second Line</td>
<td>First Line</td>
</tr>
<tr>
<td>Topical Lidocaine</td>
<td>First Line for localized peripheral NP</td>
<td>First Line for PHN with focal allodynia</td>
<td>First Line for PHN for the elderly</td>
<td>First Line for localize peripheral neuropathies</td>
<td>Second Line for localized peripheral NP⁴</td>
</tr>
<tr>
<td>Opioids Analgesics</td>
<td>Second line except in selected Circumstances⁵</td>
<td>Second Line</td>
<td>Second line for PHN and Third Line for PHN</td>
<td>Second Line</td>
<td>Third line</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Second line except in selected Circumstances⁶</td>
<td>Second Line</td>
<td>Second Line for PPN⁵</td>
<td>Second Line</td>
<td>Third line</td>
</tr>
</tbody>
</table>

¹Based on recommendations for painful polyneuropathy and postherpetic neuralgia
²Based on the recommendations for localized and diffuse peripheral neuropathies
³Duloxetine was not available in Canada per the authors at the time of this guideline
⁴The lidocaine patch was not available in Canada per the authors at the time of this guideline, however lidocaine gel was.
⁵Opioid analgesics and tramadol can be used as first-line options for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.
⁶Tramadol can be used as a second line agent for patients with painful polyneuropathy and painful exacerbations or patients with predominant coexisting non-neuropathic pain

NP = Neuropathic pain
PNP = painful polyneuropathy
PHN = postherpetic neuralgia
<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>First-line drugs</th>
<th>Second-line drugs</th>
<th>Third-line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serotonin-noradrenaline reuptake inhibitors</td>
<td>Tricyclic antidepressants</td>
<td>Pregabalin, gabapentin, gabapentin extended release or enacarbil</td>
</tr>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Effect size</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
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<tr>
<td>Tolerability and safety*</td>
<td>Moderate</td>
<td>Low-moderate</td>
<td>Moderate-high</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>Low-moderate</td>
<td>Low-moderate</td>
<td>Low-moderate</td>
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<td>Cost and resource allocation</td>
<td>Low-moderate</td>
<td>Low</td>
<td>Low-moderate</td>
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<tr>
<td>Strength of recommendation</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Neuropathic pain conditions</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

**Table 3: Summary of GRADE recommendations**
### Pharmacotherapy for painful diabetic neuropathy: Relevant comorbidities for drug selection

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Comorbidities favoring use</th>
<th>Comorbidities favoring avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td>Depression, Anxiety</td>
<td>Restless legs syndrome, Sexual dysfunction (for venlafaxine), Angle-closure glaucoma</td>
</tr>
<tr>
<td>• Duloxetine*</td>
<td></td>
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<tr>
<td>• Venlafaxine</td>
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<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>Depression, Anxiety, Insomnia</td>
<td>Cardiac disease, Prolonged QTC, Orthostatic hypotension, Sexual dysfunction, Urinary retention, Angle-closure glaucoma</td>
</tr>
<tr>
<td>• Amitriptyline</td>
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<tr>
<td>• Nortriptyline</td>
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<tr>
<td>• Desipramine</td>
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<tr>
<td>Gabapentinoid anticonvulsants</td>
<td>Restless legs syndrome, Essential tremor, Insomnia</td>
<td>Substance abuse, Peripheral edema, Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• Pregabalin*</td>
<td></td>
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<tr>
<td>• Gabapentin</td>
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</tbody>
</table>

*Approved by the US Food and Drug Administration for diabetic neuropathy.*
Nonpharmacologic options

- Use of cool or warm soaks, soft socks
- TENS
- Acupuncture
- Physical therapy and massage also have been used
Prognosis

- Most patients experience a slowly progressive course with symptoms and signs spreading proximally over time.
- Large fibers can be eventually involved.
References


• https://www.uptodate.com/contents/overview-of-polyneuropathy?search=small%20fiber%20neuropathy&source=search_result&selectedTitle=1~37&usage_type=default&display_rank=1

