

NEUROPATHIC PAIN MODULE



Complements of *painHEALTH* website

Learning objectives

By the end of this module participants should be able to:

- Know and understand the IASP definition of neuropathic pain.
- Understand the sub-classification of central and peripheral neuropathic pain.
- Understand the basic mechanisms of nerve damage and 'ectopic' nerve firing.
- Understand the main causes of neuropathic pain.
- Know that neuropathic pain may be associated with
 - *gain* of nerve function (spontaneous pain, allodynia)
 - *loss* of nerve function (numbness, motor weakness).
- Know the main descriptors of neuropathic pain:
 - shooting, stabbing, burning, electric shocks, aching
- Understand the principles of a neuropathic pain examination:
 - eliciting allodynia
 - testing for altered sensation
- Use the DN4 questionnaire to assess for possible neuropathic pain.
- Understand the management of neuropathic pain within the bio-psycho-social framework.
- Understand role of neuropathic pain medications.
 - Tricyclic antidepressants

- Gabapentinoids
 - Carbamazepine
 - Tramadol
 - Tapendadol
 - Opioids
 - Capsaicin cream
 - Lidocaine patches
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- Understand how to manage common neuropathic pain conditions:
 - Acute herpes zoster pain (shingles)
 - Post herpetic neuralgia
 - Painful diabetic peripheral neuropathy
 - Radicular leg pain (due to lumbar nerve root pathology)
 - Trigeminal neuralgia
 - Phantom limb pain

What is neuropathic pain?

- **Definition**

<p>Pain associated with a lesion or disease of the somatosensory nervous system (IASP 2008)</p>
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- The term 'neuropathic' literally means 'nerve-disease'.
 - Neuropathic pain is sometimes called '*nerve pain*' or '*neuralgia*.'
 - Neuropathic pain is sometimes difficult to diagnose and is often missed.
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- **Classification**
 - *Peripheral* neuropathic pain (PNS) (acute herpes zoster, 'sciatica')
 - *Central* neuropathic pain (CNS) (post-stroke, spinal cord injury)
 - Cortex
 - Thalamus
 - Medulla
 - Spinal cord

Who gets neuropathic pain?

- Neuropathic pain affects 5% of the general population at any one time.
 - 80% is peripheral neuropathic pain
 - 20% is central neuropathic pain
- Older adults
 - diabetic neuropathy, shingles, post-stroke
- Post-surgery or trauma patients
- Cancer patients
- Alcoholism
- HIV

The most common neuropathic pain conditions are

- Painful diabetic neuropathy
- Post herpetic neuralgia
- Radicular leg pain (sciatica)
- Post-surgical or trauma nerve injury pain
- Trigeminal neuralgia
- Chemotherapy-induced painful peripheral neuropathy
- Central pain (post-stroke, multiple sclerosis, spinal cord injury)

Common causes of neuropathic pain

- Shingles (herpes zoster virus) (*post herpetic neuralgia*).
- Diabetes (*'stocking & glove' pain, often associated with numbness & tingling*).
- Cancer, chemotherapy & radiotherapy.
- Alcoholism.
- B vitamin deficiency (B1, B6, B12).
- Nerve compression ('trapped nerves') (*'sciatica'; 'carpal tunnel syndrome'*).
- Nerve injury caused by surgery (hernia repair).
- Facial nerve pain (*trigeminal neuralgia*).
- Dental nerve pain (*severe toothache*).
- Central pain: stroke, multiple sclerosis, Parkinson's disease.
- Complex Regional Pain Syndrome (CRPS).
- Phantom pain (leg amputation).

What causes neuropathic pain?

An explanation for your patients

Neuropathic pain is due to damage or a malfunction in the 'wiring' of the nervous system. When nerves are damaged, they become super-sensitive and 'fire-off' thousands of extra pain signals, just like the shower of 'sparks' coming from a damaged power line that's fallen to the ground during a storm.

These extra nerve impulses or 'sparks' are mistakenly interpreted as 'pain' signals by the brain. Nerves anywhere in the body can be damaged by injury, surgery, 'compression' (e.g. spinal disc pressing on a nerve going to the leg [sciatica]), viruses (e.g. shingles), diabetes, auto-immune diseases (e.g. rheumatoid arthritis), vitamin deficiencies, medications, alcohol; also damage to the spinal cord (e.g. a diving or car accident) or the brain (e.g. stroke or multiple sclerosis).

Peripheral nerve damage (neuropathy)

- To understand neuropathic pain you need to understand the basic anatomy of a peripheral nerve and the processes that cause nerve damage or neuropathy.
- You also need to understand the basic classification of peripheral nerve fibre types
- A δ and C fibres transmit nociception (N.B. pain is not actually transmitted in the nervous system—it is a sensory and emotional experience that is generated in the brain).
- If A δ and C fibres are damaged, they can generate ectopic nociceptive signals that may produce neuropathic pain.

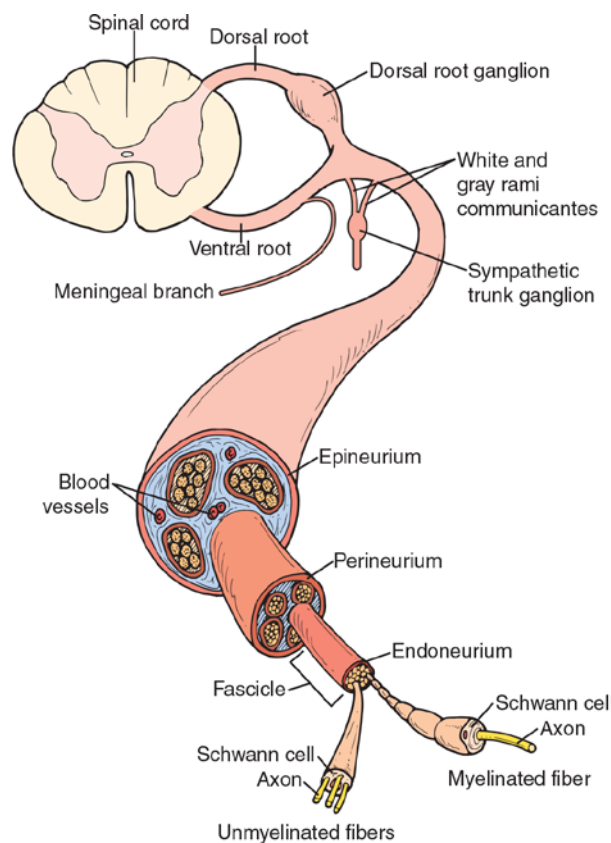


Figure 1a. Structure of a peripheral nerve.

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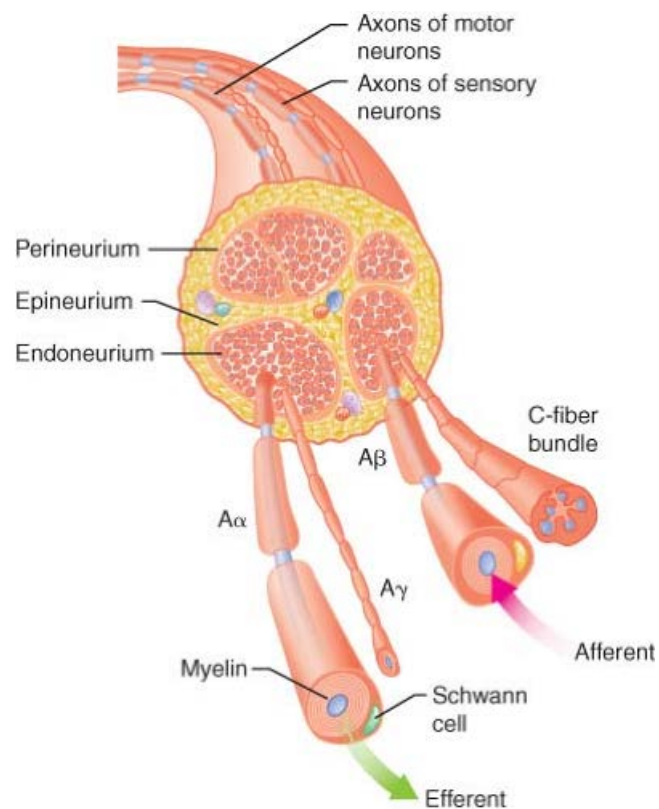


Figure 1b. Structure of a peripheral nerve.

<https://aneskey.com/wp-content/uploads/2016/06/DA4C21FF1-1.jpg>

Classification of nerve fibers

C. Classification of nerve fibers (in humans)

Fiber type	Function according to fiber type (Lloyd and Hunt types I–IV)	Diameter (μm)	Conduction rate (m/s)
A α	Skeletal muscle efferent, afferents in muscle spindles (Ib) and tendon organs (Ib)	11–16	60–80
A β	Mechanoafferents of skin (II)	6–11	30–60
A γ	Muscle spindle efferents	1–6	2–30
A δ	Skin afferents (temperature and "fast" pain) (III)		
B	Sympathetic preganglionic; visceral afferents	3	3–15
C	Skin afferents ("slow" pain); sympathetic postganglionic afferents (IV)	0.5–1.5 (unmyelinated)	0.25–1.5

(After Erlanger and Gasser)

*In the general classification the fibers are divided into types **A**, **B** and **C**, and the type **A** fibers are further subdivided into α , β , γ , δ fibers.*

Figure 2. Classification of peripheral nerve fibres.

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Classification of peripheral neuropathies

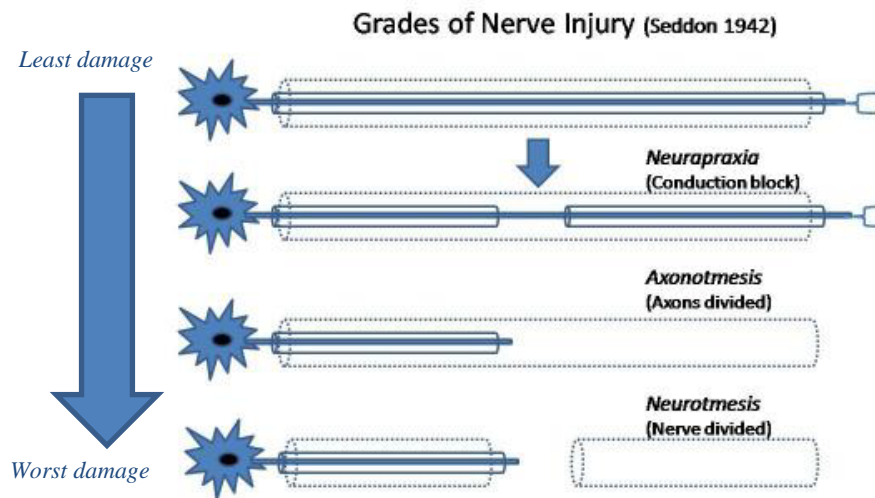
- Sensory neuropathy
- Motor neuropathy (amyotrophy)
- Mixed sensorimotor neuropathy
- Autonomic neuropathy

What parts of a peripheral nerve can be damaged?

- Nerve root
- Nerve ganglion (body)
- Axon
- Myelin sheath

What are the main types of *structural* nerve damage?

- Myelopathy (myelin 'insulation' is damaged) (neuropraxia)
- Axonopathy (axon 'wire' is damaged) (axonotmesis)
- Direct nerve injury (nerve is divided) (neurotmesis)



- Nerves can be damaged
 - mechanically (stretch, compress, cut, cancer invasion)
 - chemically (alcohol, glucose, arsenic, chemotherapy)
 - physically (radiotherapy)
 - nutritionally (B vitamins)
 - immunologically (autoimmune, infection, inflammation)
- Peripheral nerves are *metabolically-active* 'living electric wires.'
- The metabolic activity of a nerve is depend on:
 - blood supply
 - nutrition (oxygen, glucose, vitamins)
 - mitochondrial function
- Sodium channels propagate neuro-electrical signalling in nerves.
- The integrity of the *fatty myelin sheath* (insulation) is vital for normal neuronal function.
- Surrounding glia (Schwann cells) maintain the myelin sheath and act as an interface with the immune system.
- Most *inherited pain disorders* and neurological diseases are due to defects in;
 - myelin production (Fabry's)
 - Na channel function or expression (erythromelagia)
 - mitochondrial function (migraine)

Table 1. I-7 mnemonic for pathological causes of peripheral neuropathies

	Causes	Tests
Injury	Surgery, carpal tunnel, sciatica, radiotherapy	NCS, EMG, Imaging
Ingestion (toxins, drugs, nutrients)	Ethanol, B vitamins, thiamine, heavy metals, chemotherapy, drugs (e.g. statins)	FBP, diff, film Vitamins B1, B2, B6, B12 Homocysteine Vitamin E Pb, Hg, As (24 hr urine)
Internal environment	Glucose, thyroid, porphyrins, uraemia, liver dysfunction	Fasting BSL HbA1c, TFTs, U&Es, LFTs Porphyrin levels blood, urine
Immune/inflammation	Guillain-Barre syndrome, myelitis, vasculitis	ESR, CRP, Anti-CCP, ANA, ENA
Infection	Herpes zoster (shingles), Hep C, HIV, leprosy, syphilis, tic paralysis, Lyme disease	Hep C, HIV, VRDL, Lyme titres
Inherited	Fabry's disease, paroxysmal pain disorder, erythromelalgia	Genetic testing Fabry's α -galactosidase level
Invasive (cancers)	Tumour invasion, paraneoplastic, myeloma	Imaging, serum, urine protein electrophoresis

Tests in bold are 'routine' screening blood tests.

Table 2. Causes of neuropathic pain

TABLE 1. Classification of Neuropathic Pain According to Site of Major Pathology			
Pathology	Peripheral	Spinal	Brain
Genetic	Fabry neuropathy	Syringomyelia	Syringobulbia
Metabolic	Painful diabetic neuropathy	B ₁₂ myelopathy	
Traumatic	Nerve injury	Spinal cord injury	Multiple sclerosis
Vascular	Vasculitic neuropathy	Spinal cord stroke	Brain stroke
Neoplastic	Tumor compression neuropathy	Tumor compression	Tumor compression
Immunological	Guillain-Barré syndrome	Multiple sclerosis	Multiple sclerosis
Infectious	HIV, Borreliosis	Infectious myelitis	Encephalitis
Toxic	Chemotherapy neuropathy		

From *Lancet Neurol*,³ with permission.

Mayo Clin Proc. 2015 Apr;90(4):532-545. Neuropathic Pain: Principles of Diagnosis and Treatment. Gilron I et al

Clinical patterns of peripheral neuropathy

- Mononeuropathies (*isolated single nerves*)
- Mononeuritis multiplex (*multiple isolated nerves*)
- Symmetrical polyneuropathies (*stocking & glove distribution*)
- Cranial neuropathies

Neuropathological patterns of peripheral neuropathy

- Small-fibre neuropathies
- Large fibre neuropathies
- Length-dependent neuropathies
- Autonomic neuropathies

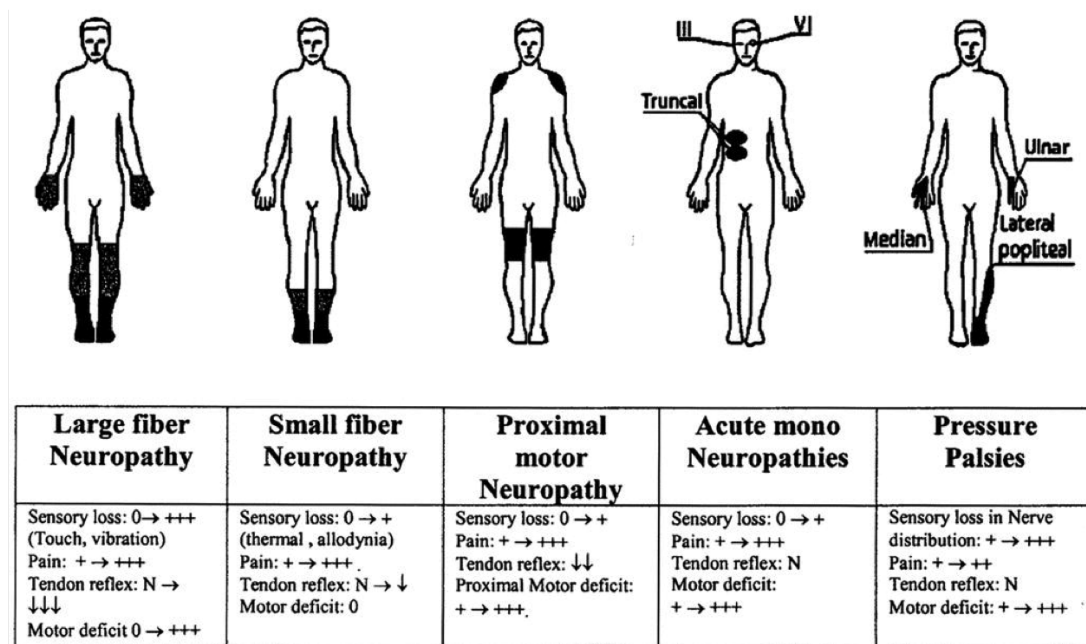


Figure 4. Classification of structural nerve damage.

<http://4.bp.blogspot.com/-F7RL3zCVjR8/VJGRnUci2aI/AAAAAAAAGwc/IQQRVe6PMCY/s1600/Clinical-Peripheral-Neuropathy.png>

Principles of neuropathology

- Nerves are complex, energy-dependent and widely dispersed tissues
- As a result they are vulnerable to damage

What keep a nerve healthy?

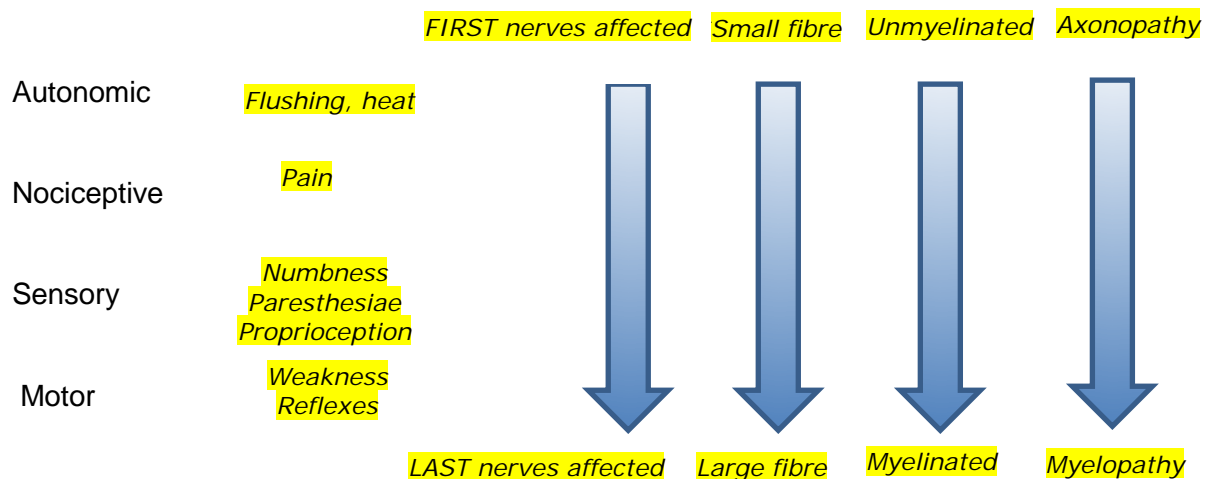
- Blood supply (*vasa vasora*)
- Nutrition (O₂, glucose, B vitamins, phospholipids, proteins)
 - neuron
 - myelin sheath
- Glia

- Neurotrophic factors (use it or lose it)
- Integrity of supporting tissues

(Mixed) peripheral nerves are composed of four (main) types of nerve fibres

- Autonomic
- Nociceptive
- Sensory
- Motor

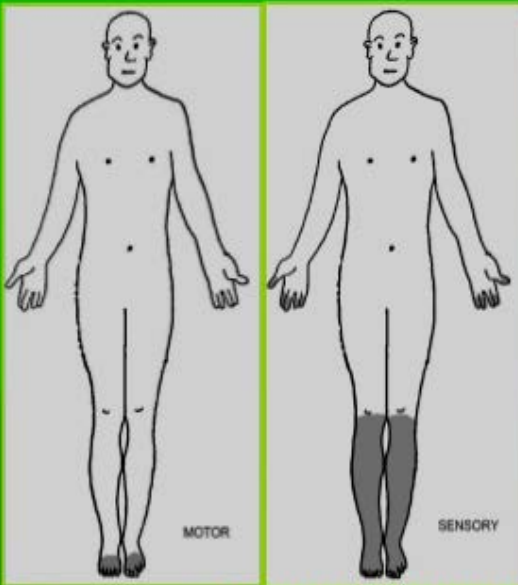
- Clinical features of a peripheral neuropathy reflect type of nerves fibres that are damaged



- Small nerve fibres (autonomic, C fibres)
 - small fibre neuropathy is common
 - vulnerable nerves (small and unmyelinated)
 - widely-dispersed and numerous (C fibres)
 - *axonopathy* in most cases
 - toxic or nutritional cause (diabetes, alcohol)
 - presents with pain and paresthesiae
 - presents with autonomic changes
 - minimal sensorimotor deficits
- **Idiopathic small fibre neuropathy**
 - 40-60 years of age
 - females 2:1

- onset in legs; trousers distribution
- burning pain at night
- Altered sensation to pinprick and cold
- mild vibration loss
- Autonomic changes (small fibres)
- Minimally abnormal NCS
- Longer nerves are more susceptible to damage
 - nerves degenerate in a **length-dependent** fashion (e.g. sural nerve)
 - further away from cell body and nutrition
 - distal-to-proximal degeneration
- Neuroimmune response with nerve damage (neurogenic inflammation)

Chronic Length Dependent Neuropathy



- Begins in toes or feet
- Stocking distribution
 - Progresses rostrally
 - Tops and bottoms of feet
- Weakness begins in ankles when sensation reaches calves

Sometimes diagnosable, Never treatable?

Gain and loss of nerve function with nerve damage

- Gain of function (pain, allodynia, paresthesiae) (*peripheral* sensitization)
- Loss of function (anaesthesia, motor weakness, autonomic)
- **Allodynia** is near-universal finding in neuropathic pain
- Pain in an area of reduced sensation is called **anaesthesia dolorosa**

- Damaged nerves become *sensitized*
 - just like a 'sparking electric wire that's fallen off a power pole'
 - they 'want' to 'keep firing' and maintain their function in the face of damage
 - they produce more Na channels, calcium channels, adrenoreceptors to 'keep firing'
- When the spinal dorsal horn is exposed to increase peripheral nerve firing (called the 'nociceptive barrage') due to nerve damage, **central sensitization** occurs which in turn amplifies the nociceptive traffic
- Gain of function (sensitization)
 - Firing is 'faster, longer, stronger, wider'
 - lower firing threshold (allodynia)
 - spontaneous firing (ectopy)
 - prolonged firing (after-polarizations)
 - increased area of firing

Clinical features and diagnosis of neuropathic pain

History: need a plausible mechanism or cause of nerve damage

- Neuropathic pain descriptors
 - spontaneous pain
 - evoked pain
 - allodynia (touch pain)
 - temperature sensitivity (especially to cold)
 - abnormal sensations
 - paresthesiae (abnormal sensations) (ants crawling)
 - dysesthesiae (unpleasant abnormal sensations)
 - phantom sensations
 - **electric qualities** (damaged wiring)
 - sparking, zapping, shooting, stabbing, shocks, lightning (lancinating)
 - burning, aching
 - sensations of heat or cold (ice cold flashes)

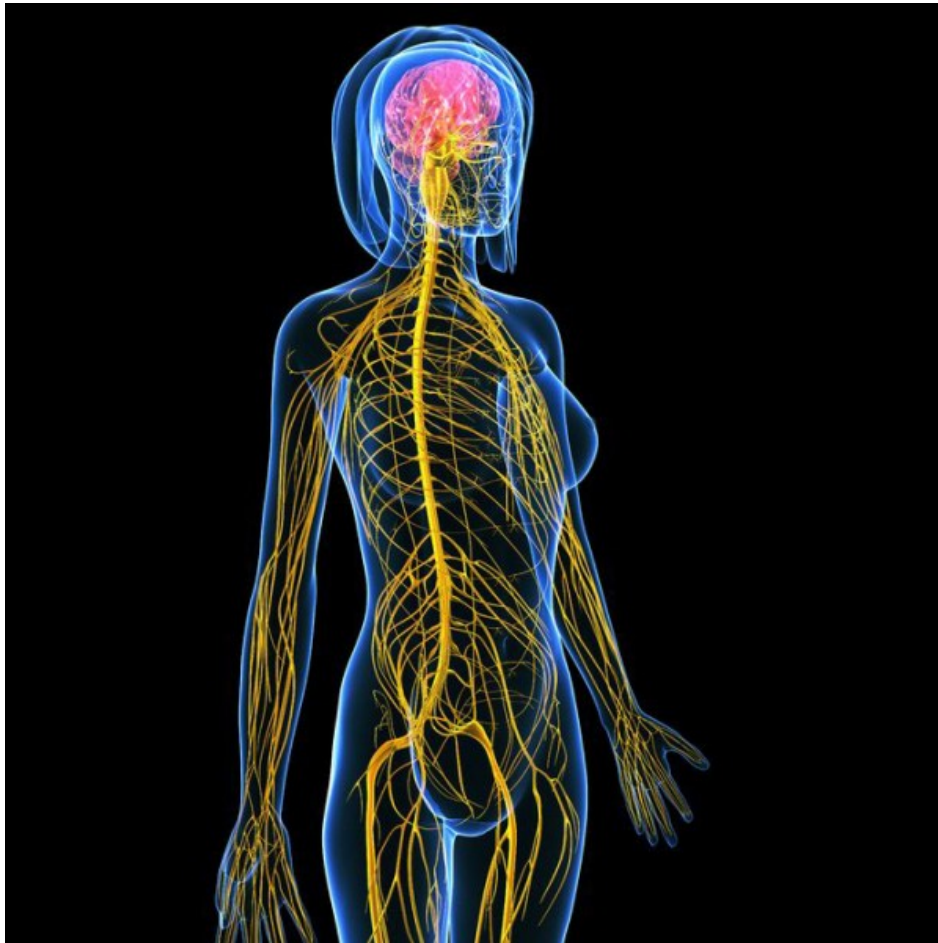
Examination: site, gain or loss of function

- Anatomy
- Peripheral nerve distributions
- Dermatomes
- Myotomes
- Cranial nerves
- CNS
- Upper *versus* lower motor neuron lesions
- QST
- POST
 - gain of function (allodynia, hyperreflexia)
 - loss of function (anaesthesia, hypoesthesia, muscle weakness, hyporeflexia)
- Autonomic, neurogenic inflammation (dermatographia)

- Neuropathic pain questionnaires
 - Combines descriptors (and in some questionnaire, physical examination findings) to determine the probability that a person has neuropathic pain.
 - The simplest and most user-friendly questionnaire is the DN4 (good sensitivity and specificity)

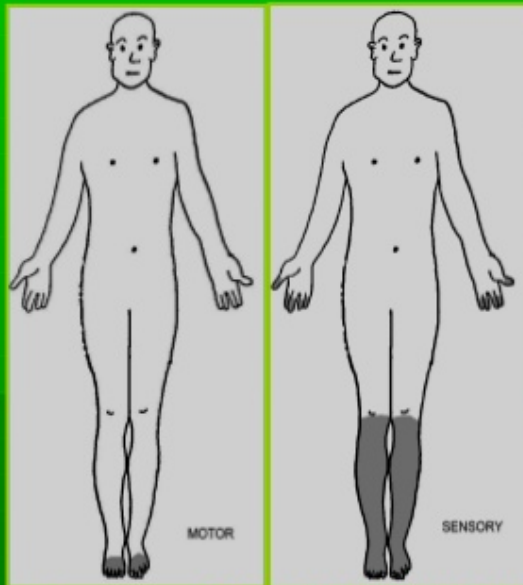
Practice tips

- Know your peripheral nerve anatomy
 - localised or regional pain,
 - always ask yourself could this be a peripheral neuropathy?
 - identify the course of nerves that run near the site of pain



<https://www.skatefins.com/wp-content/uploads/2016/03/approved-ets-centre-partners-resources-home-school-anatomy-and-physiology-refresher-course-body-studies-science-appreciate-easy-support.jpg>

Chronic Length Dependent Neuropathy

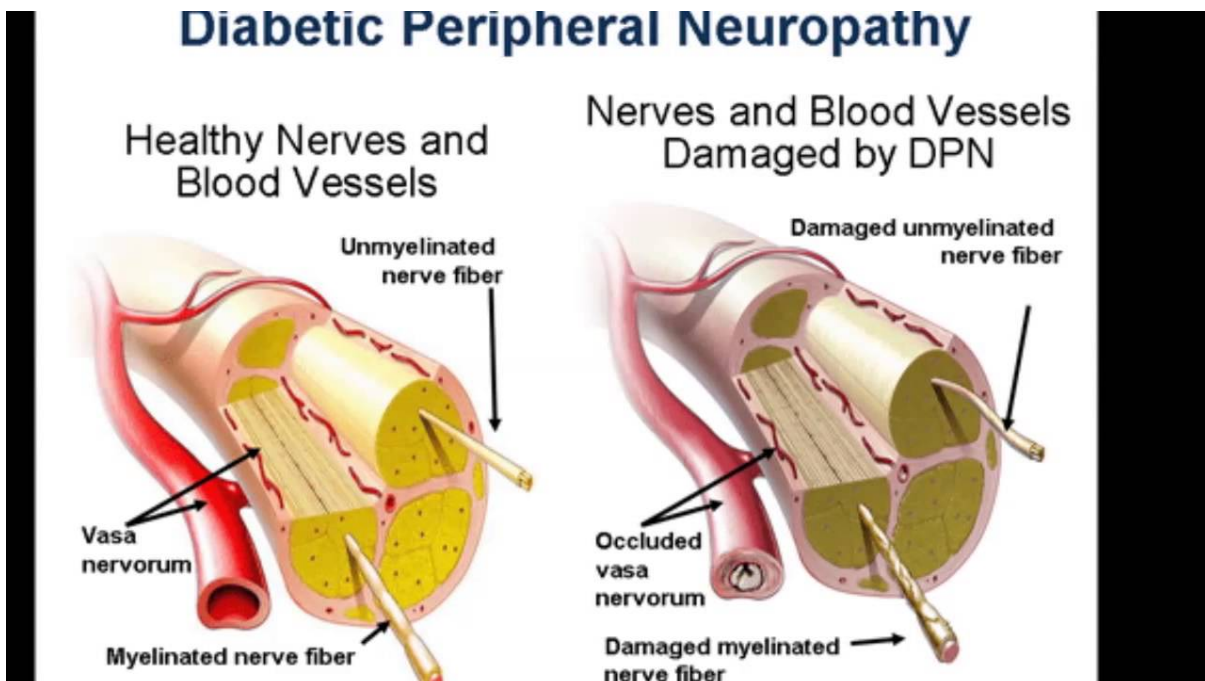


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http://www.healthhype.com/wp-content/uploads/herpeszoster_body.jpg



<https://i.ytimg.com/vi/ZiUFWjV7rTE/maxresdefault.jpg>



<https://www.dolphinmps.com/wp-content/uploads/2017/01/feet.png>

Typical Peripheral Neuropathy Symptoms

- ✓ Loss of Feeling
- ✓ Hyper Sensitivity
- ✓ Freezing
- ✓ Sharp Jabbing Pain
- ✓ Tingling
- ✓ Burning Sensation
- ✓ Numbness

A photograph of a person's feet, showing signs of peripheral neuropathy. The feet are positioned side-by-side, with the toes pointing towards the center. The skin appears dry and slightly red, with some areas of discoloration. The background is a solid orange color.

<https://i.pinimg.com/736x/21/8d/73/218d73e4524d6b7f471eb6e105edbd17--cidp-diabetic-neuropathy.jpg>

What does neuropathic pain feel like?

Pain

- Because neuropathic pain is a problem with the body's *electrical wiring (nerves)*, it often feels 'electrical' in quality.
- People usually describe 'electric shocks', 'lightning-strikes', 'buzzing', 'zapping' and 'tingling', also 'burning', 'stabbing' and 'aching'.
- Neuropathic pain often 'waxes and wanes' or comes in 'bursts', lasting from seconds to hours (remember the shower of 'sparks' from a fallen power line).

Other symptoms

Apart from *pain*, patients may also experience other symptoms in area of nerve damage;

- Touch sensitivity (called 'allodynia'), produced by lightly brushing the skin or applying pressure, heat or cold (often triggered cool breezes, air conditioning, bed sheets or hot showers).
- Allodynia feels similar to taking a hot shower when you are sunburned.
- Numbness.
- 'Pins and needles'.
- Strange sensations ('ants crawling').
- Muscle aches and spasms.
- Changes in skin temperature, colour or sweating.

Sometimes, people report severe pain in an area that is also 'numb'; this is classic for neuropathic pain and is called *anaesthesia dolorosa*.

Diagnosis

History

History

Plausible mechanism of nerve damage

Symptoms

Gain of function (spontaneous pain allodynia)

Loss of function (numbness, weakness, reflexes)

Questionnaire

DN4

Examination

Gain of function

Loss of function

Tests

Causes of nerve damage

Inflammation, Immune, infection Ingestion (nutrition, toxins)

*Blood test panel
B12, Epp, fasting BSL*

Tests of function

Nerve studies

Nerve conduction

EMG

QST

Imaging

MRI

Ultrasound

Biopsy

Skin

Saphenous nerve

Investigate

Young age

Weight loss rapid progression

Motor

Large fibre involve balance, ataxia, vibration reflexes

Sphincters

Idiopathic small fibre neuropathy

- ***50 F2:1***
- ***Legs onset***
- ***Trousers***
- ***Burning nocte***
- ***Pin prick temp change mild vibration loss***
- ***Autonomic (small fibres)***
- ***Minimally abnormal NCS***
-



<http://physioworks.com.au/images/Articles/nerve-pain.gif>

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http://painmuse.org/wp-content/uploads/causes_neurop.png

Management of neuropathic pain

- Neuropathic pain is sometimes difficult to treat and can be long-lasting, especially conditions like 'shingles'.
- A pain 'cure' is not always possible, but simple treatments often work well.

- When managing neuropathic pain, we adopt a *multi-modal, team-based approach*, combining disease management, pain medications, nerve blocks, comfort measures, pain management programmes, physiotherapy and psychology.

Prevention

Trauma and surgery

Disease prevention (diabetes, alcohol, cancer, stroke)

Zoster immunization

Neuropathic pain

Preventive analgesia

Vitamin C

Treat the cause: Manage the underlying disease, such as diabetes, vitamin deficiency, alcohol intake etc.

Glycaemic control (same as for CVS disease)

Support the nerves

Nutrition etc

Neuropathic pain medications:

- These medications work by 'damping-down' nerve firing, reducing the number of pain impulses ('sparks') coming from the irritated nerves (like a fire extinguisher).
- We use *epilepsy medications* such as pregabalin [Lyrica™] or gabapentin because epilepsy, like neuropathic pain, is caused by overactive nerve firing.
- Other medications include *tricyclic antidepressants* (TCAs) (amitriptyline [Endep™], nortriptyline [Allegron™], imipramine) and some of the newer antidepressants (SNRIs) such as duloxetine [Cymbalta™] or venlafaxine [Effexor™].
- Other epilepsy medications such as valproate [Epilim™] or phenytoin [Dilantin™] and some of the newer antidepressants (SSRIs) are *less effective* for neuropathic pain.
- *Carbamazepine* [Tegretol™] is the *most* effective medication for *nerve pain in the face*, such as trigeminal neuralgia.
- *Tramadol* or *tapentadol* are excellent neuropathic pain medications.
- Less commonly prescribed medications that may help are *clonazepam*, *baclofen* or *clonidine*.

- Occasionally, patients may need to trial morphine-based medications (called opioids) if no other treatments have been helpful.
- We recommend Norspan™ patch, oral oxycodone/naloxone (Targin™) or in some cases, methadone (needs specialist advice).
- Sometimes a combination of two neuropathic pain medications is needed.
- Because these medications work by ‘damping-down’ nerve firing in the brain, they can sometimes make you feel sleepy or dizzy, and affect thinking and memory.
- The way to deal with these side effects is to slowly build up the dose at night so the body gets used to it.

Gels, creams and local anaesthetics: Are applied to areas sensitive skin to help reduce **touch pain & skin sensitivity** (the ‘sunburn sensation’).

MENTHOL cream (4% plain) (don’t need a prescription)

- *Dencorub Arthritis Ice Therapy Gel (200g), Church & Dwight (Australia) Pty Ltd.*
Apply to areas of sensitive skin up to 4 X daily (cooling effect).
- *Michael’s Medi Rub Cream (Menthol, Eucalyptus, Emu oil and Arnica) (75 mg tube or 100 or 250g tubs).*
Apply to area of sensitive skin up to 4 X daily (cooling effect).

CAPSAICIN CREAM (need a prescription)

- *Capsaicin cream 0.075% (55g), Zostrix HP cream™.* Apply to area of sensitive skin up to 4 X daily. May cause a burning sensation when you first use it-this improves quickly; keep away from eyes or sensitive skin. Cease if significant rash or redness develops (a bit of redness or pale skin is normal).

EMLA CREAM (30 g tube) (need a prescription)

- This is a local anaesthetic cream mixture. Apply a ‘50 cent piece’ amount of the cream to the skin over the painful area (do not rub it in) and cover with a plastic dressing (‘glad wrap’ or clear adhesive dressing such as Tegaderm™); let the cream ‘melt’ under the plastic and remove after 8 hours (usually best overnight). Cease if significant rash or redness develops (a bit of redness on pale skin is normal).

LIGNOCAINE PATCH 5%: Can only obtain via a public hospital pharmacy, or a private script.

Physical therapies:

- Bandaging, stockings or ‘Tubigrip’ to protect sensitive skin from rubbing.

- A tight T-shirt or 'Tubigrip' worn over sensitive skin on the chest wall or abdomen may help (eg. shingles pain).
- Apply heat or cold packs to painful areas.
- **Physiotherapy** may help nerve pain associated with spinal nerve compression (eg. sciatica).
- **TENS** machine for ½-1 hour, up to 3 x daily, as needed.
- **Mirror box and brain re-training therapies:** Physiotherapists use these techniques in CRPS or phantom nerve pain (see: <http://www.gradedmotorimagery.com/>).

Behavioural pain management:

- Pain education, stress, anxiety and sleep management, relaxation, mindfulness.

Highly specialised treatments:

- Nerve blocks.
- Lignocaine (local anaesthetic) intravenous infusions.
- Ketamine intravenous infusions.
- High strength capsaicin patches.
- Nerve stimulator implants (expensive and only useful for a small group of selected patients)

Antineuropathics league table (Get Watg)

TCAs (amitriptyline nortriptyline, imipramine dothiepin)

SNRIs (duloxetine venlafaxine)

Pregabalin

Tramadol

Tapentadol

Opioids (Norspan, oxycodone, methadone)

Carbamazepine (TN orofacial) check Asian patient for risk Stevens Johns)

Lignocaine

Ketamine

Clonidine

Out of the box

Clonazepam
Baclofen

Ineffective

Topramate, mexilitine

Please discuss these treatment options with your doctor.

Disclaimer: The above is general information and not intended as specific clinical direction or a treatment plan. The author cannot take responsibility for outcomes associated with using information in this document.