Q&A

# Neuropathic Pain:
## A Challenging Problem

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Pain is a subjective term for an unpleasant conscious experience. Its development involves multiple levels of the nervous system from sensory endings in the skin and organs to the thalamus and cerebral cortex. Pain can be influenced by its context, for example by ongoing depression and anxiety. Nociception, in contrast, is the biological activation of specific sensory pathways in the nervous system by tissue damage. Neuropathic pain is a specific type of pain that arises from injury or disease of the nervous system.

### Robert's Case

A 65-year-old male comes to the physician complaining of burning in the soles of his feet and in his toes, especially at night. Bed clothes make the pain worse. The burning is sometimes accompanied by dull aching sensations, brief lightning-like jabs or tingling sensations in his feet. He is overweight. Two years ago, he was diagnosed with Type 2 diabetes mellitus. His hemoglobin A1C level is 8.5%. He has mild sensory loss in his toes to pinprick and light touch. His ankle reflexes are absent. The physician's diagnosis is neuropathic pain secondary to diabetic polyneuropathy (Figure 1).

### Q&A *What are the important distinctions?*

Hyperalgesia refers to the perception of an ordinarily mildly uncomfortable stimulus, either thermal or mechanical as unusually and intensely painful. Allodynia refers to the perception of a nonpainful innocuous (usually mechanical) stimulus as painful. The patient's complaint described above reports allodynia; the normally innocuous touch of bed covers triggered his pain. Neuropathic pain has recently been redefined by Treede, *et al*[1] as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system and is described as follows:

1. Pain with a distinct neuroanatomically plausible distribution
2. A history suggestive of a relative lesion or disease affecting the peripheral or central somatosensory system
3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
4. Demonstration of the relevant lesion or

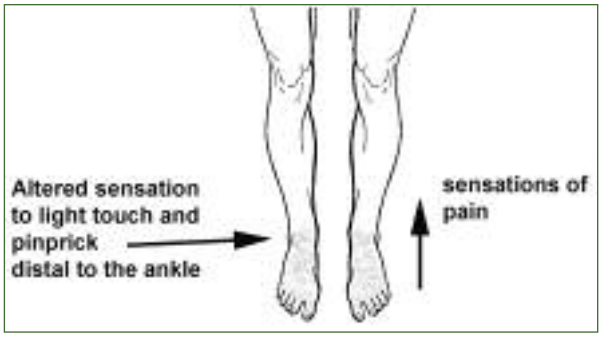


Figure 1. Stocking distribution sensory loss and pain, polyneuropathy.

disease by at least one confirmatory test Confirmatory tests can include MRI, nerve conduction studies, quantitative sensory testing and perhaps other approaches.

## Q&A What is responsible for pain?

Nociceptors, or pain receptors, are found in most body tissues with some exceptions such as within the brain. Many organs, like bones or liver, have nociceptors on the outer layers (periosteum, liver capsule). Nociceptors are thought to be free nerve endings. They can be classified as polymodal fibers, responsive to many stimuli or specific mechanical, cold, chemical or "silent" (only active after injury) sensitive fibers.

These stimuli are relayed by unmyelinated or small myelinated axons. There are a number of triggers for pain in tissues, known as algesic substances and they include protons (acid), potassium, prostaglandins, cytokines (*e.g.*, IL-6, TNF-$\alpha$, IL-1$\beta$), nitric oxide, proteases, histamine, bradykinin, ATP, substance P (a neuropeptide), nerve growth factor and others. Some of these molecules participate in "neurogenic inflammation," a process in which sensory axons release local peptides to enlarge an area of inflammation in tissues. The body also contains natural analgesic molecules that include endogenous opioids, glucocorticoids, galanin (a neuropeptide) and cannabinoids, relatives of tetrahydrocannabinol that is found in marijuana.

The intensity of a pain sensation is increased if the firing rate of the activated axons is increased or if there is a larger number of axons activated by the pain-inducing stimulus. Pain sensations are also modified by circuits in the central nervous system. For example, nociceptive axons synapse in the dorsal horn of the spinal cord and pain information is transmitted through interneurons to higher centers such as the midbrain, thalamus and sensory cortex. Functional MRI studies of cerebral activity have linked some parts of the cortex, such as the cingulate gyrus, with the quality of the pain experience. The gate theory of pain, an early attempt to understand pain circuitry, suggested that sensory input from large myelinated non-nociceptive fibers can dampen pain by activating inhibitory interneurons that in turn reduce pain impulses travelling in projection neurons to higher levels.[2] This may explain why other nonpainful sensory stimuli, such as massage or transcutaneous electrical nerve stimulation, help to relieve pain. Pain circuits can also be dampened from serotonin-containing and other axons that project downward to the dorsal horn from higher centers. Recent investigations suggest that mechanisms responsible for pain resemble those for memory.[3]

## Frequently Asked Questions

**How do I know if there is neuropathic pain?**

Typical features are burning, painful paraesthesiae (tingling), electrical sensations, lancinating (shooting) pains, tightness and relief with cold water. These symptoms should be localized in a way that indicates neurological damage.

## What is neuropathic pain?

Neuropathic pain accompanies localized injuries of peripheral nerves (*e.g.*, carpal tunnel syndrome) or generalized disorders (*e.g.*, diabetic polyneuropathy). Typical features are burning, painful paraesthesiae (tingling), electrical sensations, lancinating (shooting) pains, tightness and relief from cold water. Neurobiological changes during peripheral nerve degeneration and regeneration influence the development of neuropathic pain. For example, after axons are cut, sodium channels transported into the tips of damaged axons may cause ectopic, pain-producing discharges.[4,5] Aberrant or ectopic discharges after nerve injury not only arise from the injured axons, but also from the cell bodies of the sensory neurons housed in the dorsal root ganglia alongside the spinal canal. Both sites can act as "pacemakers" that fire inappropriate discharges up and into the central nervous system. The brain interprets these discharges as pain. Since antiepileptic agents inhibit the discharges, they can be used to treat neuropathic pain. Inflammatory cells known as microglia in the spinal cord also participate.[6] Somewhat less commonly, central nervous system lesions that involve nociceptive pathways (*e.g.*, thalamic lesions) from disorders like cerebral infarction or multiple sclerosis, can also generate pain. Neuropathic pain can also be prominent when the damage involves demyelination without axon damage, from local pain-producing inflammatory molecules. Briefly, molecular actors and pathways relevant to neuropathic pain include remodelling of sodium and calcium conductances in neurons, microglial activation, actions of cannabinoids on pain pathways, involvement of transient receptor potential channels that are responsive to capsaicin, heat or cold, endogenous opioids (natural relatives of morphine) and related molecules, purinergic (ATP) receptors, prostaglandin receptors and adrenergic pathways.

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## How is neuropathic pain treated?

Therapy for neuropathic pain involves general measures such as excluding other causes of pain, treating soft tissue injuries or ulcers, evaluating for concurrent depression and improving glycemic control in diabetics with weight loss and pharmacological intervention as required. Allodynia may be reduced through the use of a blanket cradle preventing bed covers from touching painful feet. Pharmacological therapy should be selected from those with Level 1 evi-

Table 1

**Some evidence based pharmacological therapy for neuropathic pain**

| Type of treatment | Agents | Some caveats |
|---|---|---|
| **Antiepileptic a-2 Δ-1 subunit inhibitors** | Gabapentin<br>Pregabalin | Dizziness, tiredness, edema, weight gain |
| **Older antiepileptics** | Phenytoin<br>Carbamazepine<br>Lamotrigine<br>Valproic acid | Rash, dizziness; may be more helpful for lancinating symptoms |
| **Selective serotonin and norepinephrine reuptake inhibitors** | Venlafaxine<br>Duloxetine<br>Older related agents: amitriptyline, nortriptyline | Anticholinergic side-effects and sedation from the older agents; hepatic dysfunction from duloxetine |
| **Opioids** | Tramadol<br>Oxycodone<br>Morphine (may be combined with another agent) | Risk of addiction, potential for abuse, cognitive side-effects, constipation |

dence of efficacy (Table 1). There is some limited evidence for applying capsaicin and lidocaine topically to an area of skin with neuropathic pain (such as the feet), but there is no evidence for benefit from other topical agents at this time. Dx

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