

Review (Narrative)

Neuropathic Pain

Epidemiology, Classification, Mechanisms, and Therapy

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SUMMARY

Neuropathic pain develops because of lesions or disease affecting the somatosensory nervous system either in the periphery or centrally. Examples of neuropathic pain include painful polyneuropathy, post herpetic neuralgia, trigeminal neuralgia, and post-stroke pain. Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli. Methods such as questionnaires for screening and assessment focus on the presence and quality of neuropathic pain. Basic research is enabling the identification of different pathophysiological mechanisms, and clinical assessment of symptoms and signs can help to determine which mechanisms are involved in specific neuropathic pain disorders. Management of neuropathic pain requires an interdisciplinary approach, centered on pharmacological treatment. A better understanding of neuropathic pain and, in particular, of the translation of pathophysiological mechanisms into sensory signs will lead to a more effective and specific mechanism-based treatment approach. ■

KEYWORDS Neuropathic pain; Epidemiology; Mechanisms; Classification; Treatment

Sci Insights. 2018; 2018:e000021. doi:10.15354/si.18.re002

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NEUROPATHIC Pain is a complex, chronic pain state that usually is accompanied by tissue injury. It is also often described as a shooting or burning pain. It can go away on its own but is often chronic. For many patients, the intensity of their symptoms can wax and wane throughout the day (1). Although neuropathic pain is thought to be associated with peripheral nerve problems, such as neuropathy caused by diabetes or spinal stenosis, injuries to the brain or spinal cord can also lead to chronic neuropathic pain. Sometimes it is unrelenting and severe, and sometimes it comes and goes. With neuropathic pain, the nerve fibers themselves might be damaged, dysfunctional, or injured (1, 2). These damaged nerve fibers send incorrect signals to other pain centers. The impact of a nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury. It is basically a chronic pain which is caused by the damage of central nervous system or when it becomes injured. It is always referred as an erode quality of life, when one has it. The perception of pain varies with everyone; terms such as stabbing, prickling, burning, tingling, and other descriptions have been used. Nerve pain is difficult to live with but in most individuals, it can be reduced. This observation indicates that morphine probably exerts a specific action on those brain systems that control complex behaviors like aversion and motivation (3).

HOW COMMON IS NEUROPATHIC PAIN?

It is estimated that about 7 in every 100 people over the world have persistent (chronic) neuropathic pain (3). It is much more common in older people who are more likely to develop the conditions listed above. If your doctor suspects you have neuropathic pain, he or she will ask about the pain and perform a physical examination, testing the nerves in the affected area. You may need to have blood tests, nerve conduction studies (to measure how quickly your nerves can carry electrical signals) or an MRI scan. Sometimes a nerve biopsy is needed to examine a small portion of nerve fibers for any abnormalities (4).

IDENTIFICATION OF NEUROPATHIC PAIN

Unlike other neurological conditions, identification of neuropathic pain is hard. Few, if any, objective signs are

present. Examiners must decipher and interpret a collection of words that patients use to describe their pain. Patients may describe their symptoms as sharp, dull, hot, cold, sensitive, itchy, deep, stinging, burning, or some other descriptor. Additionally, some patients may feel pain with a light touch or pressure (5).

To help identify how much pain patients may be experiencing; different scales are often used. Patients are asked to rate their pain based on a visual scale or numeric graph. Many examples of pain scales exist. Often, pictures of face depicting various degrees of pain can be helpful when patients have a difficult time describing the amount of pain they are experiencing.

WHAT CAUSES NEUROPATHIC PAIN?

There are many reasons that patients may develop neuropathic pain. However, on a cellular level, one explanation is that an increased release of certain neurotransmitters which signal pain, combined with an impaired ability of the nerves to regulate these signals leads to the sensation of pain originating from the affected region (2, 5). Additionally, in the spinal cord, the area that interprets painful signals is rearranged, with corresponding changes in neurotransmitters and loss of normally functioning cell bodies; these alterations result in the perception of pain even in the absence of external stimulation. In the brain, the ability to block pain can be lost following an injury such as stroke or trauma. Over time, further cellular damage occurs and the sense of pain persists (6).

As a matter of fact, anything that leads to loss of function within the sensory nervous system can cause neuropathic pain. As such, nerve problems from carpal tunnel syndrome or similar conditions can trigger neuropathic pain. Trauma, causing nerve injury, can lead to neuropathic pain. Other conditions, which can predispose patients to developing neuropathic pain, include diabetes, vitamin deficiencies, cancer, HIV, stroke, multiple sclerosis, shingles, and cancer treatments.

Various conditions can affect nerves and may cause neuropathic pain as one of the features of the condition. Some of these include the following:

- Trigeminal neuralgia.
- Pain following shingles (post herpetic).
- Diabetic neuropathy - a nerve disorder that develops in some people with diabetes.

- Phantom limb pain following surgical removal (amputation) of a limb.
- Multiple sclerosis.
- Pain following chemotherapy.
- HIV infection.
- Alcoholism.
- Cancer.
- Atypical facial pain.
- Various other uncommon nerve disorders.

MECHANISMS OF NEUROPATHIC PAIN

Neuropathic pain is associated with abnormal tactile and thermal responses that may be extraterritorial to the injured nerve. Importantly, tactile allodynia and thermal hyperalgesia may involve separate pathways, since complete and partial spinal cord lesions have blocked allodynia, but not hyperalgesia, after spinal nerve ligation (SNL). Tactile allodynia is likely to be mediated by large diameter A beta fibers, and not susceptible to modulation by spinal opioids, whereas hyperalgesia is mediated by unmyelinated C-fibers, and is sensitive to blockade by spinal opioids (7). Additionally, abnormal, spontaneous afferent drive in neuropathic pain may contribute to NMDA-mediated central sensitization by glutamate and by non-opioid actions of spinal dynorphin (5). Additionally, abnormal, spontaneous afferent drive in neuropathic pain may contribute to NMDA-mediated central sensitization by glutamate and by non-opioid actions of spinal dynorphin. Correspondingly, SNL elicited elevation in spinal dynorphin content in spinal segments at and adjacent to the zone of entry of the injured nerve along with signs of neuropathic pain. Antiserum to dynorphin A or MK-801 given spinally blocked thermal hyperalgesia, but not tactile allodynia, after SNL, and restored diminished morphine ant nociception. Finally, afferent drive may induce descending facilitation from the rostroventromedial medulla (RVM) (8). Blocking afferent drive with bupivacaine also restored lost potency of PAG morphine, as did CCK antagonists in the RVM. This observation is consistent with afferent drive activating descending facilitation from the RVM, and thus diminishing opioid activity, and may underlie the clinical observation of limited responsiveness of neuropathic pain to opioids.

Pain modulatory networks in the brain play an active role in controlling spinal nociceptive responses so that pain perception is influenced by our state of arousal,

attention and expectation. This Supraspinal pain modulation is mediated by networks distributed throughout the limbic system and midbrain that exert their control at the level of the dorsal horn of the spinal cord, via anti- and pro-nociceptive descending pathways arising in the RVM. Usually this pain experience begins in early life and this stimulation activates even the youngest newborn infant brain but the importance of this early experience upon adult pain processing has been neglected in theories of pain. Responses to pain in early life are different from those seen in adults; thermal and mechanical thresholds are significantly lower in young animals and humans, and behavioral responses to noxious stimulation are uncoordinated and exaggerated. The Supraspinal control of spinal nociceptive reflexes is slow to develop over the postnatal period. A major contribution to RVM pain control arises from the central actions of endogenous opioids (9).

Component nuclei of the pain-modulating circuit are linked through the release of endogenous opioids, which influence pain modulation by acting upon opiate receptors within the circuit, including the RVM (7-9). Endogenous opioids are known to play a role in synaptogenesis and in brain development, their role in the growth and development of pain pathways is not known. Opioid networks may have a trophic role in the maturation of Supraspinal pain control and that the transition from descending facilitation to inhibition in the preadolescent period is dependent upon endogenous opioid signaling in the immature brain.

CLASSIFICATIONS OF NEUROPATHIC PAIN

Phantom Limb Syndrome

This rare condition occurs when an arm or a leg has been removed because of illness or injury, but the brain still gets pain messages from the nerves that originally carried impulses from the missing limb. These nerves now misfire and cause pain. Basically, neuropathic pain is the type of pain that all people have had at some point. It is caused by actual, or potential, damage to tissues (10). For example, a cut, a burn, an injury, pressure or force from outside the body, or pressure from inside the body (for example, from a tumor) can all cause this pain. The reason we feel pain in these situations is because tiny nerve endings become activated or damaged by the injury, and this sends pain messages to the brain via nerves.

Trigeminal Neuralgia

Trigeminal neuralgia is a disorder of the trigeminal nerve - the nerve that supplies sensation to the face and controls some of the muscles involved in chewing. It causes episodes of severe facial pain that last from a couple of seconds to several minutes (1).

Post-Herpetic Neuralgia

About one in every 5 people with shingles (a painful rash also known as herpes zoster) develops post-herpetic neuralgia - ongoing pain in the area that was affected by the rash. It occurs when the shingles virus damages the underlying nerves, and the resulting pain can last for months or years (4).

Allodynia

This means that the pain comes on, or becomes worse, with a touch or stimulus that would not normally cause pain (8). For example, a slight touch on the face may trigger pain if you have trigeminal neuralgia, or the pressure of the bedclothes may trigger pain if you have diabetic neuropathy.

Hyperalgesia

This means that you get severe pain from a stimulus or touch that would normally cause only slight discomfort. For example, a mild prod on the painful area may cause intense pain (6).

Paraesthesia

This means that you get unpleasant or painful feelings even when there is nothing touching you, and no stimulus (9). For example, you may have painful pins and needles, or electric shock-like sensations.

TREATING THE UNDERLYING CAUSE

If this is possible, it may help to ease the pain. For example, if you have diabetic neuropathy then good control of the diabetes may help to ease the condition. If you have cancer, if this can be treated then this may ease the pain. The severity of the pain often does not correspond with the seriousness of the underlying condition. For example, pain following shingles (post herpetic neuralgia) can cause a severe pain, even though there is no rash or sign of infection remaining (10).

MEDICATIONS USED TO TREAT NEUROPATHIC PAIN

If the doctor suspects that the patient has a neuropathic pain, he or she will examine the patient by conducting proper interview that when the pain occurs and how long it lasts. They perform a physical examination, conducting the nerve tests in the affected areas. Patients may need to have blood tests and nerve conduction studies, to examine how much time the nerves take to carry the electrical signals. Sometimes a nerve biopsy is also needed to examine the abnormalities. In general, if one has neuropathic pain, your doctor will most likely suggest him/her try regular pain medicines such as aspirin, paracetamol or a non-steroidal anti-inflammatory drug (NSAID) to start with. But while they are worth trying, these medicines may not always relieve neuropathic pain (11).

To diagnose neuropathic pain, a doctor will conduct an interview and physical exam. He or she may ask questions about how you would describe your pain, when the pain occurs, or whether anything specific triggers the pain. The doctor will also ask about your risk factors for neuropathic pain and may also request both blood and nerve tests (12).

You may have already tried traditional painkillers such as paracetamol or anti-inflammatory painkillers such as ibuprofen that you can buy from pharmacies. However, these are unlikely to ease neuropathic pain very much in most cases.

Tricyclic Anti-Depressant Medicines

An antidepressant medicine in the tricyclic group is a common treatment for neuropathic pain. It is not used here to treat depression. Tricyclic antidepressants ease neuropathic pain separate to their action on depression. It is thought that they work by interfering with the way nerve impulses are transmitted. There are several tricyclic antidepressants, but amitriptyline is the one most commonly used for neuralgic pain (11).

A tricyclic antidepressant may ease the pain within a few days, but it may take 2-3 weeks. It can take several weeks before you have maximum benefit. Some people give up on their treatment too early. It is best to persevere for at least 4-6 weeks to see how well the antidepressant is working.

Tricyclic antidepressants sometimes cause drowsiness as a side effect. This often eases in time. To try to

avoid drowsiness, a low dose is usually started at first and is then built up gradually if needed. Also, the full daily dose is often taken at night because of the drowsiness side effects. A dry mouth is another common side effects. Frequent sips of water may help with a dry mouth. See the leaflet that comes with the medicine packet for a full list of possible side effects (12).

Other Anti-Depressant Medicines

An antidepressant called duloxetine has also been shown in research trials to be good at easing neuropathic pain. Duloxetine has been found to be a good treatment for diabetic neuropathy and is now often used first-line for this condition. Duloxetine is not classed as a tricyclic antidepressant but as a serotonin and norepinephrine reuptake inhibitor (SNRI) (11, 12). It may be tried for other types of neuropathic pain if a tricyclic antidepressant has not worked so well, or has caused problematic side effects. The range of possible side effects caused by duloxetine is different to those caused by tricyclic antidepressants.

Opiate Painkillers

Opiate painkillers, such as codeine, morphine and related medicines, are the stronger traditional painkillers. As a rule, they are not used first-line for neuropathic pain. This is partly because there is a risk of problems of drug dependence, impaired mental functioning and other side effects with the long-term use of opiates (13).

Tramadol is a painkiller that is like opiate but has a distinct method of action that is different to other opiate painkillers. Tramadol can be used for short-term treatment of neuropathic pain. Tramadol should not be used for prolonged treatment.

Capsaicin Cream

This is sometimes used to ease pain if the above medicines do not help, or cannot be used because of problems or side effects. Capsaicin is thought to work by blocking nerves from sending pain messages. Capsaicin cream is applied 3-4 times a day. It can take up to 10 days for a good pain-relieving effect to occur (14).

Capsaicin can cause an intense burning feeling when it is applied, if it is used less than 3-4 times a day, or if it is applied just after taking a hot bath or shower. However, this side effect tends to ease off with regular use. Capsaicin cream should not be applied to broken or in-

flamed skin. Wash your hands immediately after applying capsaicin cream (15).

Other kinds of treatments can also help with neuropathic pain:

- Physical therapy
- Working with a counselor
- Relaxation therapy
- Massage therapy
- Acupuncture

Unfortunately, neuropathic pain often responds poorly to standard pain treatments and occasionally may get worse instead of better over time. For some people, it can lead to serious disability. A multidisciplinary approach that combines therapies, however, can be a very effective way to provide relief from neuropathic pain.

SIDE EFFECTS AND TITRATION OF MEDICATIONS

For most of the medicines listed above it is common practice to start at a low dose at first. This may be sufficient to ease the pain but often the dose needs to be increased if the effect is not satisfactory. This is usually done gradually and is called titrating the dose (13, 16). Any increase in dose may be started after a certain number of days or weeks - depending on the medicine. Your doctor will advise as to how and when to increase the dose if required; also, the maximum dose that can be taken for each medicine. We need to find the lowest dose required to ease the pain. This is because the lower the dose, the less likely the side effects will be troublesome. Possible side effects vary for the different medicines used. A full list of possible side effects can be found with information in the medicine packet. Some people don't develop any side effects; some people are only mildly troubled by side effects that are OK to live with. However, some people are troubled quite badly by side effects. Tell your doctor if you develop any troublesome side effects (17). A switch to a different medicine may be an option if this occurs.

CONCLUDING REMARKS

Neuropathic pain is thorny problem faced by many medical specialties. Although great progress has made on the understanding of the underlying mechanisms, it is not that easy for the physician to find the most effec-

tive medications for individualized therapy. Currently available medications for neuropathic pain only have approximately ~50% effectiveness. Further work is nec-

essary to identify more reliable and efficient medications for neuropathic pain. ■

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Zhao.
Critical revision of the manuscript for important intellectual content: Zhao.
Statistical analysis: N/A.
Obtained funding: N/A.
Administrative, technical, or material support: Zhao.
Study supervision: Zhao.

Conflict of Interest Disclosures: The authors declared no competing interests of this manuscript submitted for publication.

Acknowledgement: N/A.

Funding/Support: N/A.

Role of the Funder/Sponsor: N/A.

How to Cite This Paper: Zhao C, Cheng Y, Yu J, Li L, A L, Shi C, Wang S, Cui S. Neuropathic pain: Epidemiology, classification, mechanisms, and therapy. *Sci Insigt.* 2018; 2018:e000021.

Digital Object Identifier (DOI):
<http://dx.doi.org/10.15354/si.18.re002>.

Article Submission Information: Received, January 08, 2018; Revised: January 26, 2018; Accepted: January 29, 2018.

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