

Pathophysiology of Pain — Classification, Types, and Management

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Pain management is an inseparable part of modern patient care. This article expatiates various aspects of the pathophysiology of pain focusing on definition, pain team, complex regional pain syndrome, neuropathic pain, and the latest concept of “NO” analgesics.



Definition and Pathophysiology of Pain

The word pain takes origin from the Latin *poena* which connotes penalty and has the same root as the word patient, or the sufferer of poena.

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

The Oxford Pocket Dictionary definition is as follows: “[Pain is a] strongly unpleasant bodily sensation such as is caused by illness or injury.”

Types of Pain Axons

Peripheral nerves, both motor and sensory, are grouped by size and myelination. Type A fibers are large and myelinated, thus fast conducting. There are 4 types of A fibers:

- **A-alpha fibers** are the primary receptors of the muscle spindle and Golgi tendon organ.
- **A-beta fibers** act as secondary receptors of the muscle spindle and contribute to cutaneous mechanoreceptors.
- **A-delta fibers** are **free nerve endings that conduct painful stimuli** related to pressure and temperature.
- **A-gamma fibers** are typically motor neurons that control the intrinsic activation of the muscle spindle.

There are also middle-sized, thinly myelinated fibers, or **Type B fibers**. They are devoted to autonomic information.

Lastly, **Type C fibers** are unmyelinated and slow. They are considered polymodal because they can often respond to combinations of thermal, mechanical, and chemical stimuli.

Nociceptors have two different types of axons.

The first are the **A-delta fiber axons**. They are myelinated and can allow an action potential to travel at a rate of about 20 m/s towards the CNS.

The other type is the more slowly conducting **C fiber axons**. These only conduct at speeds of around 2 m/s. This is due to the non-myelination of the axon.

As a result, pain comes in two phases. The first phase is mediated by the fast-conducting A-delta fibers and the second part is due to C fibers. The pain associated with the A-delta fibers can be associated to an initial **extremely sharp** pain. The second phase is a more prolonged and slightly less intense feeling of pain as a result of the acute damage.

Pathophysiology of pain

Nociceptive receptors in the periphery respond to pH, ATP, and ligands to create afferent nerve conduction. The cell bodies of these neurons are located in either the dorsal horn and dorsal root ganglia of the spinal cord or the trigeminal ganglia that carry pain fibers from the face.

This nociceptive fiber (located in the periphery) is a first-order neuron. The cells in the dorsal horn are divided into physiologically distinct layers called laminae. Different fiber types form synapses in different layers, and use either glutamate or substance P as the neurotransmitter. A-delta fibers form synapses in laminae 1 and 5; C fibers connect with neurons in lamina 2.

After reaching the specific lamina within the spinal cord, the first order nociceptive project to second-order neurons that cross the midline at the anterior white commissure. The second-order neurons then send their information to the [brain stem](#), and specifically to the thalamus via the lateral spinothalamic tract (both pain and temperature). In the ventral posterior nucleus of the thalamus, the information is processed. The thalamus is where the pain is thought to be brought into perception; it also aids in pain suppression and modulation.

From the thalamus, the stimulus is sent to the cerebral cortex in the brain via fibers in the posterior limb of the internal capsule. The somatosensory cortex decodes nociceptor information to determine the exact location of pain; this is also where proprioception is brought into consciousness.

As there is an ascending pathway to the brain that initiates the conscious realization of pain, there also is a descending pathway which modulates pain sensation. The brain can request the release of specific chemicals that can have analgesic effects which can reduce or inhibit pain sensation. **The area of the brain that stimulates the release of these hormones is the hypothalamus.**

The hypothalamus signals for the release of mediators and hormones, such as opioid peptides, norepinephrine, glycine, and GABA, that make pain suppression more effective; some of these include sex hormones.

Peri-aqueductal grey (with hypothalamic hormone aid) hormonally signals the reticular formation's raphe nuclei to produce serotonin that inhibits the pain nuclei and the laminar nuclei of the dorsal horn of the spinal cord. This is why stimulation of peri-aqueductal grey reduces pain. **It is also the location of opioid receptors.**

Thus the **'pain matrix'** in the brain comprises of the insular cortex, anterior cingulate cortex, thalamus, hypothalamus, amygdala, and the periaqueductal grey matter.

The neuromatrix theory of pain conceptualizes pain as a multidimensional phenomenon; a result of characteristic 'neurosignature' patterns of nerve impulses generated by a vast aggregation of neural networks—the 'body-self neuromatrix'—in the brain.

Classification of Pain

Pain can be of various types. Common nomenclature is as follows:

- Sharp
- Crushing
- Burning
- Cramping
- Gassy
- Throbbing, cutting, aching, dull, deep, pinching, slashing, pinpoint, continuous, spasm, tearing, lancing, knifing, etc.

The International Association for the Study of Pain (IASP) classification is as follows:

- Region of the body involved (e.g., abdomen and lower limbs)
- System whose dysfunction may be causing the pain (e.g., nervous and gastrointestinal)
- Duration and pattern of occurrence
- Intensity and time since onset. About intensity, it is common to ask the patient to grade his/her current pain with a scale from 0 to 10. 0 means no pain, and 10 means the worst pain he/she ever experienced. This helps with dosing and frequency of opiates administration.
- Cause

An alternative classification stated by Woolf segregates pain in 3 classes:

- Nociceptive pain
- Inflammatory pain

- Pathological pain

Types of pain

Pain can be categorized as follows:

Type	Duration	Characteristic	Management
Acute pain	< 3 months	Severe, but usually manageable such as surgical pain, pain from injuries	Managed effectively by anesthesiologist acute pain service (APS) with opioids, NSAID's, acetaminophen, local anesthetics
Transitional pain	3-6 months	Not easily diagnosed, needs aggressive treatment to prevent transition to chronic	This is the last chance, in many cases, for really effective elimination of the pain.
Chronic pain/long-lasting pain	> 3-6 months	Difficult to treat, personality changes, drug-seeking	

Chronic Pain Management

Pain is reported by 30–50% of cancer patients on treatment and by almost 70–90% of those with a terminal disease. Incidence of chronic pain appears to be independent of race, culture, economic status. Disabling pain is more common than cancer or heart disease.

Meant for evaluation of the psychosocial state of a person, the **multidimensional pain inventory (MPI)** is an inventory designed to assess chronic pain.

Evidence suggests the following statistics:

- 2% have disabling pain
- 12% have severe pain
- 30% of adults have 'chronic pain' at any given time.

Chronic pain is the vice of modern life. The WHO (World Health Organization) has formulated a **"3-step ladder" for cancer pain relief** in adults. A 2-step ladder has been developed for the pediatric population.

This approach recommends administering the **right drug at the right dose at the right time**, rather than "on schedule" drug administration. It is relatively inexpensive and 80–90% effective.

The **Pain Relief Ladder** can be tabulated as:

Step in the ladder	Treatment options
First step	Non-opioid analgesic (aspirin and paracetamol) with/without adjuvant therapy (additional drugs to calm fears and anxiety)
Second step (if pain is persistent/ worsened)	Opioid for mild to moderate pain (codeine) with/ without non-opioid and adjuvant therapy
Third step (if pain is persistent/ worsened after the second tier of management)	Opioid for moderate to severe pain (morphine) with/without non-opioid and adjuvant therapy

Surgical intervention is considered if these drugs are not completely effective.

The key instrumental components in our armamentarium against chronic pain are **analgesics**.

Pain neurotransmission-simplified

Nociceptive receptors in the periphery respond to pH, ATP, and ligands to create afferent nerve conduction to the dorsal horn and dorsal root ganglia of the spinal cord, brainstem, thalamus, hypothalamus, and the cortex.

The modulation occurs at all levels and is mediated by opioid peptides, norepinephrine, glycine, and GABA.

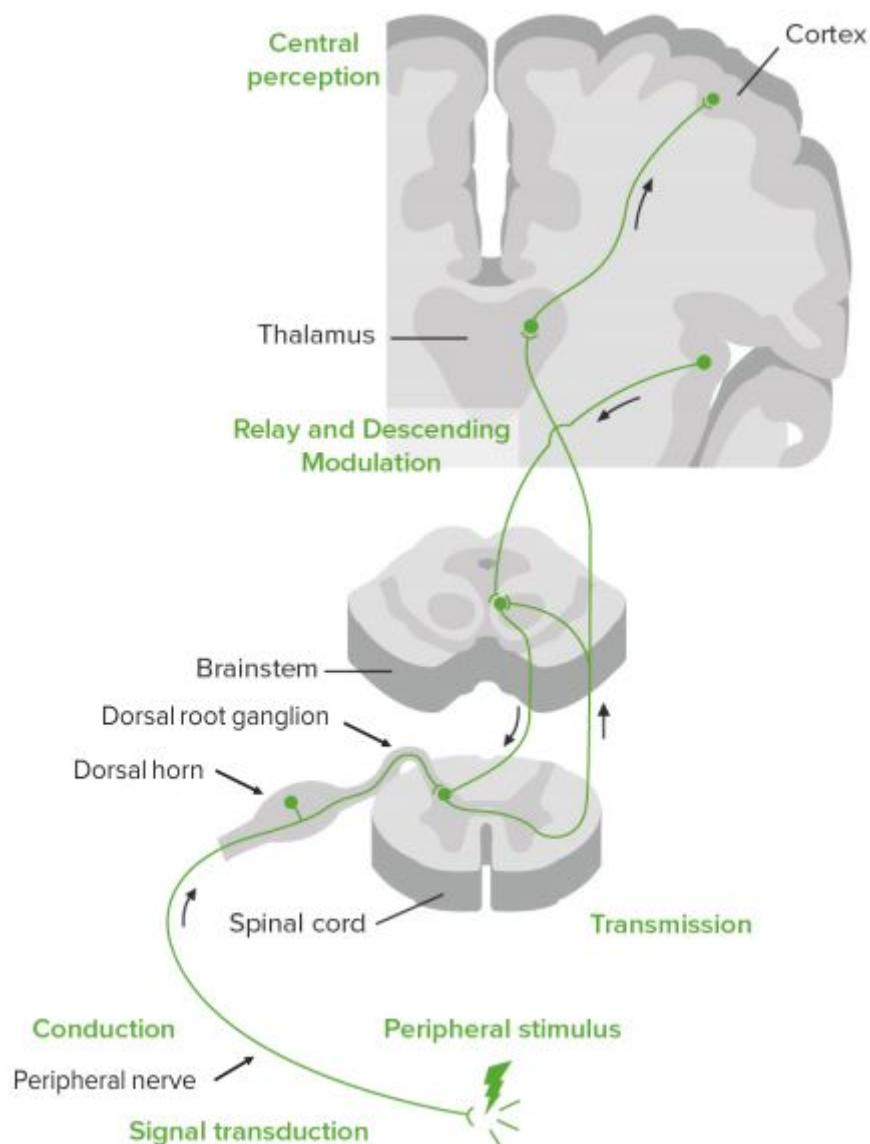


Image: Chronic pain management, by Lecturio

Opiates

Opiates are drugs from natural sources; opioids are manufactured drugs.

To date, **opiates** epitomize the most potent and reliable analgesic agents. They have a complementary unmitigated beneficial role in ameliorating anxiety, inducing mild sedation and creating a sense of well-being, often bordering on euphoria.

They react with opiate and opioid receptors, which are mu, delta, and kappa, in the brain. **Potent analgesia is determined by the affinity and efficacy of drugs for the mu receptors only.** Mu receptors are a class of opioid receptors with a high affinity for enkephalins and beta-endorphins. The activation of the mu-opioid receptor inhibits the release of substance P from the incoming first-order neurons and, in turn, inhibits the activation of the second-order neuron that is responsible for transmitting the pain signal up the spinothalamic tract to the ventroposterolateral nucleus (VPL) of the thalamus. Drug interactions in different parts of the nervous system are summarized as follows:

Site of action	Mechanism of action
Brain	alter mood in response to pain
Brainstem	stimulate the release of inhibitory signals
Spinal cord	inhibit the primary afferent activity
Peripheral sites	inhibit afferent response

However, no drug comes without **adverse effects**. The troublesome downside for opiates is more of **psychosocial nature**. They are:

- Illegal activity in drug procurement
- **Drug abuse**—overdose, withdrawal, tolerance, and dependence
- Infections secondary to shared needles.

Short term use of opiates (**less than 3 months**) is the unequivocal remedy for pain, but there is significant reluctance in chronic pain management, particularly when not caused by malignancy. The most potent opioids are the ones most likely to be abused.

Management of chronic non-malignant pain (or pain lasting for more than 3 months) is associated with the development of tolerance and addiction.

Irrespective the type of chronic pain, we have no substitutes for opioids.

Pain team concept

Institutional models, clinical pathways, and consultation services are 3 surrogate formulations for cancer pain management.

A clinical pathway is an integrated institutionalized model. Pain consultation service is an establishment by itself.

Evidence indicates that only a multidisciplinary 'pain team' can be successful in treating chronic pain. The crucial members are:

- The family
- Nurse (nurse-clinicians)
- Social worker
- Neurosurgeon
- Radiologist
- Occupational therapist
- Pastoral care
- Pharmacist
- Clinical pharmacologist
- Anesthesiologist
- Psychiatrist
- Psychologist
- Physiotherapist

For **obstetrical pain**, patient, partner, coach, midwife, obstetrician and last but not least the anesthesiologist comprise the team.

Acute pain such as that caused by surgery or injury can be managed by anesthesiology but there should be access to other professionals as well.

Complex Regional Pain Syndrome (CRPS)

CRPS has been variously named as reflex sympathetic dystrophy, causalgia, Sudeck atrophy, algodystrophy, post-traumatic dystrophy, and shoulder-hand syndrome.

Introduced by the International Association for the Study of Pain (IASP) in 1994, CRPS encompasses various **post-traumatic neuropathic pain conditions of the limbs**.

The original documentation of CRPS is witnessed in Ambroise Pare's report from the 16th century portraying the pain and contractures of King Charles 9th after a blood-letting procedure.

CRPS is characterized as types 1 and 2. The only discriminating element is the presence of a peripheral nerve injury in type 2.

Modified clinical diagnostic criteria (Budapest criteria) are used to diagnose CRPS.

Its natural history is subdivided into 3 progressive phases based on the duration of symptoms:

Stage	Description
Stage I (acute stage: 0-3 months)	Pain/sensory dysfunction (e.g., hyperalgesia, allodynia, or increased response of neurons following normally non-painful, often repetitive, stimulation, signs of vasomotor abnormalities, and prominent edema and sudomotor disturbance, (> anything that stimulates the sweat glands)
Stage II (dystrophic stage: 3-9 months)	Marked pain/sensory dysfunction, continued evidence of vasomotor disturbance, with significant motor/trophic changes
Stage III (atrophic stage: 9-18 months)	Decreased pain/sensory complaints continued vasomotor abnormality, significantly aggravated motor/trophic changes

CRPS is an uncommon transition to chronic pain disease with a prevalence of < 2%.

CRPS can be initiated by relatively minor insults (soft tissue injuries or minor fractures). Peripheral sensitization occurs, resulting in allodynia and hyperalgesia. Characterized by severe pain, swelling, and skin changes; it can culminate in a completely non-functional limb requiring amputation—the most painful long-term measure (42 out of 50 on the McGill Pain Score).

It may be associated with '**neurogenic inflammation**'. It is often associated with tooth sensitivity (allodynia and changes to the central nervous system as a manifestation of adapting to constant pain signals (neuroplasticity).

The etiopathogenesis of CRPS is largely unearthed. The involvement of multiple mechanisms is an accepted fact. The prominence of classic signs of inflammation (**edema**, redness, hyperthermia, and impaired function) in the early stages of CRPS makes inflammation the most conspicuous pathway.

Few other significant modalities of interest are:

- Disturbances in cutaneous innervation (lower density of small fibers—C and A-

alpha)

- Central and peripheral sensitization
- Dysfunction of the sympathetic nervous system
- Diminished circulating catecholamine
- Lower systemic levels of anti-inflammatory cytokines (interleukin-10)
- Aggravated levels of local and systemic inflammatory cytokines (TNF- α , interleukin-1, -2, and -6).
- Genetic factors (HLA-b-62 and HLA-DQ-8 alleles)
- Psychological factors (anxiety, anger, and depression)

CRPS requires a very **aggressive team approach** to therapy. The therapy varies and needs to be customized as per the intensity of patient symptomatology. Various modalities available can be summarized as follows:

Intensity of CRPS	Treatment options
Mild	Physiotherapy
Moderate	Physiotherapy, adjuvant analgesics like gabapentin and/or antidepressants.
Severe with sympathetic dysfunction	Physiotherapy facilitated by regional anesthetic blockade
Chronic refractory pain	Long term multi-faceted approach with physiotherapy, pain ameliorating measures, psychosocial support

Neuropathic Pain

Injury, ischemia, trauma or inflammation to peripheral nerves and CNS leading to functional and structural changes in the pathways lead to neuropathic pain. It is a sudden, unexpected, episodic, fleeting, and shock-like pain.

Nerve regeneration after an injury can produce a nidus of intense pain. A '**neuroma**', a nodule of exquisite sensitivity, can sometimes be palpated.

Neuropathic pain is a challenge to confront and requires a full pain team.

Neuromodulation (spinal cord stimulation) sometimes helps but treatment failures are very common. **Algorithms** designed to take into consideration the entire patient's constellation of pain-related symptoms and signs are often instrumental in successful patient management.

Though unfortunate, in some cases the patient must be taught to "**live with the pain**".

It is common in **diabetics** but can also occur with no apparent cause.

"NO" Analgesic Approach

Analgesics have revolutionized patient management in many ways. But in human hands, these drugs are fraught with complications such as **drug overdose, toxicity, side-effects, withdrawal, tolerance, dependence, abuse, and systemic complications**.

Hence, the latest rank in the hierarchical management of pain is "NO" analgesics.

Terminal cancer patients and those with advanced diseases are positively encouraged to resort to adjuvant therapies like **music therapy, yoga, and meditation**.

The evidence might not be unequivocal, but many patients seek solace and comfort in these modalities.

Summary

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

Pain is carried by fast A-delta fibers and slow C fibers to the thalamus and from there to many areas of the brain. The hypothalamus and the peri-aqueductal grey modulate and may block pain by activating mu receptors.

Pain has been variously classified mainly to facilitate treatment by the intensity of patient symptomatology, disease etiology, and response to treatment.

Today's era recommends a 'pain team' approach: a multidisciplinary approach to target the multiple facets of pain and ultimately bring about better patient care and satisfaction.

The WHO recommends a 3-step ladder graded approach for pain relief in cancer patients.

Complex regional pain syndrome encompasses varying post-traumatic neuropathic pain conditions of the limbs. The diagnosis is mainly clinical with an early, aggressive, and multi-faceted approach.

Neuropathic pain results from structural changes in neuronal pathways as a result of injury, ischemia, trauma or inflammation. Common in diabetics, it is sudden, unexpected, shock-like, severe, fleeting pain. Drugs used to alleviate neuropathic pain include gabapentin and antidepressants. While a substantial proportion of patients resort to surgical intervention as a result of treatment failure with medications, some must be taught to live with it.

Cancer patients are encouraged to try adjuvant therapies to augment medical therapy and bring about calm and comfort to the patient. Prominent ones are music therapy, yoga, and meditation.

Review Questions

The correct answers can be found below the references.

1. Which of the following is not included in the 2nd step treatment options of the WHO pain ladder?

- A. Morphine
- B. Codeine
- C. Aspirin
- D. Paracetamol

2. Complex regional pain syndrome type 1 differs from type 2 in what?

- A. Duration of injury
- B. Clinical symptoms
- C. Involvement of nerve injury in type 2
- D. Management options

3. Which of the following is not included in neuropathic pain treatment options?

- A. Gabapentin
- B. Electroconvulsive treatment (ECT)

- C. Surgical intervention
- D. Physiotherapy

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Correct answers: 1A, 2C, 3B

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Notes