ANESTHESIOLOGY 250

Integrated Clinical Clerkship I in Anesthesiology

(Introduction to Pain Management)

SELF-INSTRUCTIONAL MODULES

Academic Year 2021-2022

Prepared by:

Dominic D. Villa, MD, DPBA, DPBPM

ANESTHESIOLOGY 250

Despite medical advances, pain remains a frequent and undertreated symptom among patients. When the UP College of Medicine announced that it will be adopting an organ system integrated curriculum, the Philippine General Hospital Department of Anesthesiology revised its 4 week anesthesia course offered to the year level 6 medical students. Recognizing that all types of physicians play a vital role in the prevention, diagnosis and management of acute and persistent pain, such revision in the curriculum was viewed as an opportunity to educate medical students regarding the foundation of pain management. The 4-week course was divided into a one-week rotation during year level 5 (introduction to pain), 2 weeks during year level 6 (perioperative anesthesia) and 1 week during year level 7 (post-operative care). This revision was intended to instill among medical students an in-depth understanding and appreciation of the short-term and long-term benefits and ill-effects of not addressing pain promptly and adequately. Prior to this revision, the year level 6 medical students only received a one-hour lecture on acute pain during their 4-week rotation. This was complemented with their exposure in the perioperative course in the operating room.

Starting Academic Year 2004 – 2005, Anesthesiology 250 (Clinical Clerkship I in Anesthesiology) was offered to the year level 5 medical students (Integrated Clinical Clerks). Anesthesiology 250 is a 1-week course. The course is an introduction to pain management with emphasis on the basic foundations such as the definition of pain, pathophysiology of pain, types of pain, pain assessment and modalities of treatment.

Since we are now experiencing COVID-19 times, learning activities of the medical students have been modified. Face-to face lectures, small group discussions, exposure to pain patients (Pain Clinic: chronic pain; Outpatient OR Post-Anesthesia Care Unit and inpatient Post-Anesthesia Care Unit: acute pain) as well as observation of performance of regional anesthesia techniques for perioperative use have been replaced by Online learning.

These Self-Instructional Modules will reinforce your lectures in video format and hopefully will enhance your learning and appreciation of the course.

EKVILLA

MODULES 1, 2, and 3:
DEFINITION, ANATOMY and PHYSIOLOGY OF PAIN

Pain is not just a sensory modality but an experience.

Dr. John J. Bonica, considered the "Father of Pain Management" and Founder of the International Association of the Study of Pain in 1973 coined the operational definition of pain as

- *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."*

This definition recognizes the interplay between the objective, physiological sensory aspects of pain and its subjective, emotional, and psychological components. The response to pain can be highly variable among different individuals as well as in the same person at different times.

- The dictionary defines pain as physical suffering associated with disease, injury, or other bodily disorder. It is also a form of mental distress.

- Margo McCaffery – an American registered nurse and pioneer of the field of pain management nursing defined pain as: *"whatever the experiencing person says it is, existing whenever and wherever the person says it does."*

Terms used in pain management

- Allodynia - Perception of an ordinarily non-noxious stimulus as pain
- Analgesia - Absence of pain perception
- Anesthesia - Absence of all sensation
- Anesthesia dolorosa - Pain in an area that lacks sensation
- Dysesthesia - Unpleasant or abnormal sensation with or without a stimulus
- Hypalgesia (hypoalgesia) - Diminished response to noxious stimulation (ex, pinprick)
- Hyperalgesia - Increased response to noxious stimulation
- Hyperesthesia - Increased response to mild stimulation
- Neuralgia - Pain in the distribution of a nerve or a group of nerves
- Paresthesia - Abnormal sensation perceived without an apparent stimulus

ASK YOURSELF….

1. Have I felt pain before? How did I react? *(Pain is one of the most universal feelings like LOVE. It is always unpleasant…unless you are a masochist)*
2. What is this shooting, electric-like pain radiating down my leg when I bend? *(It could be sciatica, a form of neuralgia.)*

Anatomy, Physiology, and Neurochemistry of Somatosensory Pain Processing

Pain is conducted along **three neuronal pathways** that transmit noxious stimuli from the periphery to the cerebral cortex (Figure 1).

The cell bodies of **primary** afferent neurons are located in the *dorsal root ganglia*, which lie in the vertebral foramina at each spinal cord level. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the spinal cord.

In the *dorsal horn*, the primary afferent neuron synapses with a **second-**order neuron whose axon crosses the midline and ascends in the contralateral spinothalamic tract to reach the thalamus.

Second-order neurons synapse in *thalamic nuclei* with **third-**order neurons, which in turn send projections through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex (Figure 2).

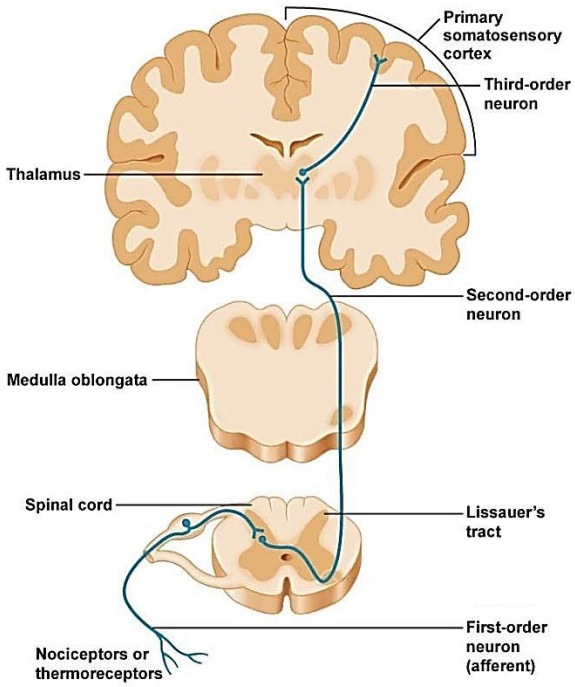


Figure 1. 3 Neuron Pain Pathway

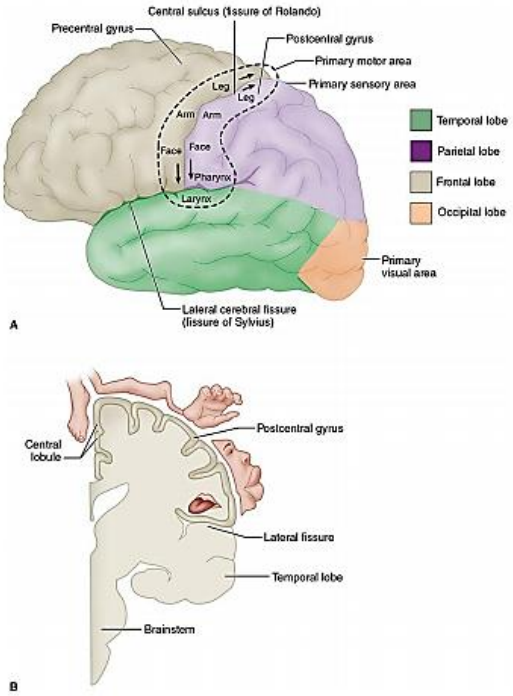


Figure 2. Lateral (A) and coronal (B) views of the brain show the location of the primary sensory cortex.

First-Order Neurons

The majority of first-order neurons send the proximal end of their axons into the spinal cord via the dorsal (sensory) spinal root at each cervical, thoracic, lumbar, and sacral level. Some unmyelinated afferent (C) fibers have been shown to enter the spinal cord via the ventral nerve (motor) root, accounting for observations that some patients continue to feel pain even after transection of the dorsal nerve root (rhizotomy) and report pain following ventral root stimulation.

Once in the dorsal horn, in addition to synapsing with second-order neurons, the axons of first-order neurons may synapse with interneurons, sympathetic neurons, and ventral horn motor neurons.

Pain fibers originating from the head are carried by the trigeminal (V), facial (VII), glossopharyngeal (IX), and vagal (X) nerves.

- The **gasserian** ganglion contains the cell bodies of sensory fibers in the ophthalmic, maxillary, and mandibular divisions of the *trigeminal nerve.*
- The **geniculate** ganglion contains cell bodies of first-order afferent neurons of the *facial nerve.*
- The **superior and petrosal** ganglia contain cell bodies of the *glossopharyngeal nerve.*
- The **jugular** ganglion (somatic) and the **ganglion nodosum/nodose ganglion** (visceral) contains cell bodies of the *vagus nerve.*

Second-Order Neurons

As afferent fibers enter the spinal cord, they segregate according to size, with large, myelinated fibers becoming medial, and small, unmyelinated fibers becoming lateral. Pain fibers may ascend or descend one to three spinal cord segments in **Lissauer's tract** before synapsing with second-order neurons in the gray matter of the ipsilateral dorsal horn. In many instances they communicate with second-order neurons through interneurons.

Spinal cord gray matter was divided by Rexed into 10 laminae (Figure 3 and Table 1). *The first six laminae*, which make up the **dorsal horn**, receive all afferent neural activity and represent the principal site of modulation of pain by ascending and descending neural pathways.

Second-order neurons are either **nociceptive-specific** or **wide dynamic range (WDR) neurons**.

Nociceptive- specific neurons serve only noxious stimuli, but WDR neurons also receive nonnoxious afferent input from Aβ, Aδ, and C fibers. Nociceptive-specific neurons are arranged somatotopically in lamina I and have discrete, somatic receptive fields; they are normally silent and respond only to high-threshold noxious stimulation, poorly encoding stimulus intensity.

WDR neurons are the most prevalent cell type in the dorsal horn. Although they are found throughout the dorsal horn, WDR neurons are most abundant in lamina V. During repeated stimulation, **WDR neurons** characteristically increase their firing rate exponentially in a graded fashion **("wind-up"),** even with the same stimulus intensity. They also have large receptive fields compared with nociceptive-specific neurons.

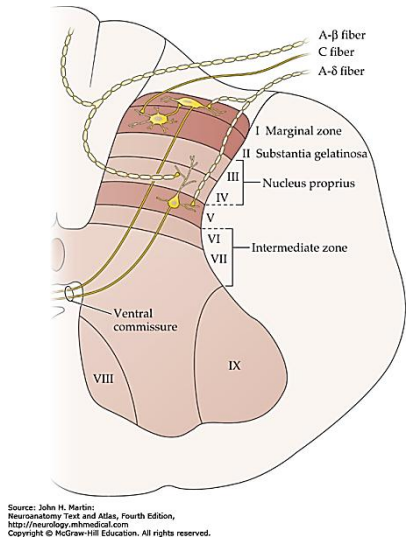


Figure 3. Rexed's spinal cord laminae.

Lamina	Predominant Function	Input	Name
I	Somatic nociception thermoreception	Aδ, C	Marginal layer
II	Somatic nociception thermoreception	C, Aδ	Substantia gelatinosa
III	Somatic mechanoreception	Aβ, Aδ	Nucleus proprius
IV	Mechanoreception	Aβ, Aδ	Nucleus proprius
V	Visceral and somatic nociception and mechanoreception	Aβ, Aδ, (C)	Nucleus proprius WDR neurons[1]
VI	Mechanoreception	Aβ	Nucleus proprius
VII	Sympathetic		Intermediolateral column
VIII		Aβ	Motor horn
IX	Motor	Aβ	Motor horn
X		Aβ, (Aδ)	Central canal

[1]WDR, wide dynamic range.

Table 1. Spinal cord laminae.

Most nociceptive C fibers send collaterals to, or terminate on, second-order neurons in laminae I and II, and, to a lesser extent, in lamina V. In contrast, nociceptive Aδ fibers synapse mainly in laminae I and V, and, to a lesser degree, in lamina X.

- Lamina I responds primarily to noxious (nociceptive) stimuli from cutaneous and deep somatic tissues.
- Lamina II, also called the **substantia gelatinosa**, contains many interneurons and is believed to play a major role in processing and modulating nociceptive input from cutaneous nociceptors. It is also of special interest because it is believed to be *a major site of action for opioids.*
- Laminae III and IV primarily receive nonnociceptive sensory input.
- Laminae VIII and IX make up the anterior (motor) horn.
- Lamina VII is the intermediolateral column and contains the cell bodies of preganglionic sympathetic neurons.

Visceral afferents terminate primarily in lamina V, and, to a lesser extent, in lamina I. These two laminae represent points of central convergence between somatic and visceral inputs. Lamina V responds to both noxious and nonnoxious sensory input and receives both visceral and somatic pain afferents. *The phenomenon of convergence between visceral and somatic sensory input is manifested clinically as* **referred pain**. Compared with somatic fibers, visceral nociceptive fibers are fewer in number, more widely distributed, proportionately activate a larger number of spinal neurons, and are not organized somatotopically.

A. The Spinothalamic Tract

The axons of most second-order neurons cross the midline close to their dermatomal level of origin (at the anterior commissure) to the contralateral side of the spinal cord before they form the spinothalamic tract and send their fibers to the thalamus, the reticular formation, the nucleus raphe magnus , and the periaqueductal gray.

The spinothalamic tract, which is classically considered the *major pain pathway*, lies anterolaterally in the white matter of the spinal cord (Figure 4). This ascending tract can be divided into a lateral and a medial tract.

- The **lateral** spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries *discriminative aspects of pain*, such as location, intensity, and duration.
- The **ventral/anterior** spinothalamic (paleospinothalamic) tract projects to the medial thalamus and is responsible for mediating the *autonomic and unpleasant emotional perceptions* of pain.

Some spinothalamic fibers also project to the periaqueductal gray and thus may be an important link between the ascending and descending pathways. Collateral fibers also project to the reticular activating system and the hypothalamus; these are likely responsible for the arousal response to pain.

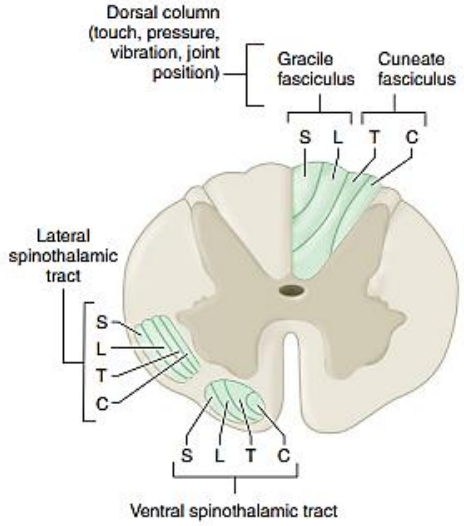


Figure 4. A cross section of the spinal cord showing the spinothalamic and other ascending sensory pathways.

B. Alternate Pain Pathways

As with epicritic sensation, pain fibers ascend diffusely, ipsilaterally, and contralaterally; some patients continue to perceive pain following ablation of the contralateral spinothalamic tract, and therefore other ascending pain pathways are also important.

- The **spinoreticular tract** is thought to mediate arousal and autonomic responses to pain.
- The **spinomesencephalic** tract may be important in activating antinociceptive, descending pathways, because it has some projections to the periaqueductal gray.
- The **spinohypothalamic** and spinotelencephalic tracts activate the hypothalamus and evoke emotional behavior.
- The **spinocervical** tract ascends uncrossed to the lateral cervical nucleus, which relays the fibers to the contralateral thalamus; this tract is likely a major alternative pathway for pain.
- Lastly, some fibers in the dorsal columns (which mainly carry light touch and proprioception) are responsive to pain; they ascend medially and ipsilaterally.

C. Integration with the Sympathetic and Motor Systems

Somatic and visceral afferents are fully integrated with the skeletal motor and sympathetic systems in the spinal cord, brainstem, and higher centers. Afferent dorsal horn neurons synapse both directly and indirectly with anterior horn motor neurons. These synapses are responsible for **the reflex muscle activity**—whether normal or abnormal—that is associated with pain. *(this allows you to withdraw your hand from a hot stove)*

In a similar fashion, synapses between afferent nociceptive neurons and sympathetic neurons in the intermediolateral column result in reflex sympathetically mediated vasoconstriction, smooth muscle spasm, and the release of catecholamines, both locally and from the adrenal medulla. *(this explains the sympathetic response to pain)*

Third-Order Neurons

Third-order neurons are located in the thalamus and send fibers to somatosensory areas I and II in the postcentral gyrus of the parietal cortex and the superior wall of the sylvian fissure, respectively. Perception and *discrete localization* of pain take place in these cortical areas. Although most neurons from the lateral thalamic nuclei project to the primary somatosensory cortex, neurons from the intralaminar and medial nuclei project to the anterior cingulate gyrus and are likely involved in mediating *the suffering and emotional components* of pain.

PHYSIOLOGY OF NOCICEPTION

A variety of mechanical, thermal, electrical, or chemical stimuli can result in the sensation and perception of pain. Information about these painful or noxious stimuli is transmitted to higher brain centers by receptors and neurons that are often distinct from those that carry innocuous somatic sensory information. The mammalian somatosensory system is subserved by four groups of afferent fibers differentiated by their anatomy, rate of transmission, and sensory modality transduced (Table 2).

Type of Nerve Fibre	Information Carried	Myelin Sheath?	Diameter (micrometers)	Conduction Speed (m/s)
A-alpha	proprioception	myelinated	13 - 20	80 - 120 
A-beta	touch	myelinated	6 - 12	35 – 90 
A-delta	pain (mechanical and thermal)	myelinated	1 - 5	5 – 40 
C	pain (mechanical, thermal, and chemical)	non-myelinated	0.2 - 1.5	0.5 - 2 

Table 2. Primary Afferent Fibers and Their Function

1. Nociceptors

Nociceptors are characterized by a high threshold for activation and encode the intensity of stimulation by increasing their discharge rates in a graded fashion. Following repeated stimulation, they characteristically display delayed adaptation, sensitization, and after discharges.

Noxious sensations can often be broken down into two components:

- a fast, sharp, and well-localized sensation (“first pain”), which is conducted with a short latency (0.1 s) by **Aδ fibers** (tested by pinprick);
- and a slower onset, duller, and often poorly localized sensation (“second pain”), which is conducted by **C fibers**.

In contrast to epicritic sensation, which may be transduced by specialized end organs on the afferent neuron (eg, pacinian corpuscle for touch), protopathic sensation is transduced mainly by free nerve endings. Most nociceptors are free nerve endings that sense heat and mechanical and chemical tissue damage. Types include

(1) mechanonociceptors , which respond to pinch and pinprick,

(2) silent nociceptors, which respond only in the presence of inflammation, and

(3) polymodal mechanoheat nociceptors. The last are most prevalent and respond to excessive pressure, extremes of temperature >42°C and noxious substances such as bradykinin, histamine, serotonin (5-hydroxytryptamine or 5-HT), H+, K+, some prostaglandins, capsaicin, and possibly adenosine triphosphate.

At least two nociceptor receptors (containing ion channels in nerve endings) have been identified, TRPV1 and TRPV2. Both respond to high temperatures. Capsaicin stimulates the TRPV1 receptor. Polymodal nociceptors are slow to adapt to strong pressure and display heat sensitization.

Cutaneous Nociceptors

Nociceptors are present in both somatic and visceral tissues. Primary afferent neurons reach tissues by traveling along spinal somatic, sympathetic, or parasympathetic nerves. Somatic nociceptors include those in skin (cutaneous) and deep tissues (muscle, tendons, fascia, and bone), whereas visceral nociceptors include those in internal organs. The cornea and tooth pulp are unique in that they are almost exclusively innervated by nociceptive Aδ and C fibers.

Deep Somatic Nociceptors

Deep somatic nociceptors are less sensitive to noxious stimuli than cutaneous nociceptors but are easily sensitized by inflammation. The pain arising from them is characteristically dull and poorly localized. Specific nociceptors exist in muscles and joint capsules, and they respond to mechanical, thermal, and chemical stimuli.

Visceral Nociceptors

Visceral organs are generally **insensitive tissues** that mostly contain ***silent nociceptors***. Some organs appear to have specific nociceptors, such as the heart, lung, testis, and bile ducts. Most other organs, such as the intestines, are innervated by polymodal nociceptors that respond to smooth muscle spasm, ischemia, and inflammation. These receptors generally do not respond to the cutting, burning, or crushing that occurs during surgery. A few organs, such as the **brain, lack nociceptors** altogether; however, the brain's meningeal coverings do contain nociceptors.

Like somatic nociceptors, those in the viscera are the free nerve endings of primary afferent neurons whose cell bodies lie in the dorsal horn. These afferent nerve fibers, however, frequently travel with efferent sympathetic nerve fibers to reach the viscera. Afferent activity from these neurons enters the spinal cord between T1 and L2.

Nociceptive C fibers from the esophagus, larynx, and trachea travel with the vagus nerve to enter the nucleus solitarius in the brainstem.

Afferent pain fibers from the bladder, prostate, rectum, cervix and urethra, and genitalia are transmitted into the spinal cord via parasympathetic nerves at the level of the S2–S4 nerve roots.

Though relatively few compared with somatic pain fibers, fibers from primary visceral afferent neurons enter the cord and synapse more diffusely with single fibers, often synapsing with multiple dermatomal levels and often crossing to the contralateral dorsal horn.

2. Chemical Mediators of Pain

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neurons subserving pain (Table 3). Many, if not most, of these neurons contain more than one neurotransmitter, which are simultaneously released. The most important of these *peptides* are **substance P** and **calcitonin gene-related peptide (CGRP)**. **Glutamate** is the most important *excitatory amino acid*. Substance P is an 11 amino acid peptide that is synthesized and released by first-order neurons both peripherally and in the dorsal horn. Also found in other parts of the nervous system and the intestines, it facilitates transmission in pain pathways via neurokinin-1 receptor activation. In the periphery, substance P neurons send collaterals that are closely associated with blood vessels, sweat glands, hair follicles, and mast cells in the dermis. Substance P sensitizes nociceptors, degranulates histamine from mast cells and 5-HT from platelets, and is a potent vasodilator and chemoattractant for leukocytes. Substance P–releasing neurons also innervate the viscera and send collateral fibers to paravertebral sympathetic ganglia; intense stimulation of viscera, therefore, can cause direct postganglionic sympathetic discharge. Both opioid and α2 -adrenergic receptors have been described on or near the terminals of unmyelinated peripheral nerves. Although their physiological role is not clear, the latter may explain the observed analgesia of peripherally applied opioids, particularly in the presence of inflammation.

Neurotransmitter	Receptor[1]	Effect on Nociception
Substance P	Neurokinin–1	Excitatory
Calcitonin gene-related peptide		Excitatory
Glutamate	NMDA, AMPA, kainate, quisqualate	Excitatory
Aspartate	NMDA, AMPA, kainate, quisqualate	Excitatory
Adenosine triphosphate (ATP)	P_1, P_2	Excitatory
Somatostatin		Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	μ, δ, κ	Inhibitory
β-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α_2	Inhibitory
Adenosine	A_1	Inhibitory
Serotonin	5-HT_1 (5-HT_3)	Inhibitory
γ-Aminobutyric acid (GABA)	A, B	Inhibitory
Glycine		Inhibitory

[1]NMDA, *N*-methyl-D-aspartate; AMPA, 2-(aminomethyl)phenylacetic acid; 5-HT, 5-hydroxytryptamine.

Table 3. Major neurotransmitters mediating or modulating pain.

3. Modulation of Pain

Modulation of pain occurs peripherally at the nociceptor, in the spinal cord, and in supraspinal structures. This modulation can *either inhibit* (suppress) or *facilitate* (intensify) pain.

Peripheral Modulation of Pain

Nociceptors and their neurons display sensitization following repeated stimulation. Sensitization may be manifested as an enhanced response to noxious stimulation or a newly acquired responsiveness to a wider range of stimuli, including non-noxious stimuli.

A. Primary Hyperalgesia

Sensitization of nociceptors results in

- a decrease in threshold,
- an increase in the frequency response to the same stimulus intensity,
- a decrease in response latency,
- and spontaneous firing even after cessation of the stimulus (after discharges).

Such sensitization commonly occurs with injury and following application of heat. Primary hyperalgesia is mediated by the release of *noxious substances* from damaged tissues. This is the ***"Inflammatory Soup".***

- **Histamine** is released from mast cells, basophils, and platelets
- **serotonin** is released from mast cells and platelets.
- **Bradykinin** is released from tissues following activation of factor XII. Bradykinin activates free nerve endings via specific B1 and B2 receptors.
- **Prostaglandins** are produced following tissue damage by the action of phospholipase A 2 on phospholipids released from cell membranes to form arachidonic acid. The cyclooxygenase (COX) pathway then converts the latter into endoperoxides, which in turn are transformed into prostacyclin and prostaglandin E2 (PGE 2). PGE 2 directly activates free nerve endings, whereas prostacyclin potentiates the edema from bradykinin. The lipoxygenase pathway converts arachidonic acid into hydroperoxy compounds, which are subsequently converted into leukotrienes. The role of the latter is not well defined, but they appear to potentiate certain types of pain. Pharmacological agents such as acetylsalicylic acid (ASA, or aspirin), acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs) ***produce analgesia by inhibition of COX***. The analgesic effect of corticosteroids is likely the result of inhibition of prostaglandin production through blockade of phospholipase A 2 activation.

B. Secondary Hyperalgesia

Neurogenic inflammation, also called **secondary hyperalgesia**, plays an important role in peripheral sensitization following injury. It is manifested by the **"triple response (of Lewis)"** of a red flush around the site of injury (flare), local tissue edema, and sensitization to noxious stimuli.

Secondary hyperalgesia is primarily due to *antidromic* release of substance P (and probably CGRP). Substance P degranulates histamine and 5-HT, vasodilates blood vessels, causes tissue edema, and induces the formation of leukotrienes.

The neural origin of this response is supported by the following findings: (1) it can be produced by electrical stimulation of a sensory nerve, (2) it is not observed in denervated skin, and (3) it is diminished by injection of a local anesthetic.

Capsaicin applied topically in a gel, cream, or patch *depletes substance P* and diminishes neurogenic inflammation, and is useful for some patients with postherpetic neuralgia.

Central Modulation of Pain

A. Facilitation

At least three mechanisms are responsible for **central sensitization in the spinal cord:**

1. ***Wind-up and sensitization of second-order neurons.*** WDR neurons increase their frequency of discharge with the same repetitive stimuli and exhibit prolonged discharge, even after afferent C fiber input has stopped.
2. ***Receptor field expansion.*** Dorsal horn neurons increase their receptive fields such that adjacent neurons become responsive to stimuli (whether noxious or not) to which they were previously unresponsive.
3. ***Hyperexcitability of flexion reflexes***. Enhancement of flexion reflexes is observed both ipsilaterally and contralaterally. Neurochemical mediators of central sensitization include substance P, CGRP, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), angiotensin, and galanin, as well as the excitatory amino acids l -glutamate and l -aspartate. These substances trigger changes in membrane excitability by interacting with G protein–coupled membrane receptors on neurons. Glutamate and aspartate play important roles in wind-up, via activation of N -methyl- d -aspartate (NMDA) and other receptor mechanisms, and in the induction and maintenance of central sensitization. Activation of NMDA receptors also induces nitric oxide synthetase, increasing formation of nitric oxide. Both prostaglandins and nitric oxide facilitate the release of excitatory amino acids in the spinal cord. Thus, COX inhibitors such as ASA and NSAIDs have important analgesic actions in the spinal cord.

B. Inhibition

Transmission of nociceptive input in the spinal cord can be inhibited by segmental activity in the cord itself, as well as by descending neural activity from supraspinal centers.

1. Segmental inhibition —Activation of large afferent fibers subserving sensation inhibits WDR neuron and spinothalamic tract activity. Moreover, activation of noxious stimuli in noncontiguous parts of the body inhibits WDR neurons at other levels, which may explain why pain in one part of the body inhibits pain in other parts. These two phenomena support a ***"gate" theory for pain*** processing in the spinal cord.

ASK YOURSELF…..

Why do feel less pain when we shake or rub an injured body part?

Large-diameter Aβ fibers are nonnociceptive (do not transmit pain stimuli) and inhibit the effects of firing by Aδ and C fibers.

In transcutaneous electrical nerve stimulation (TENS), nonnociceptive fibers are selectively stimulated with electrodes in order to produce this effect and thereby lessen pain.

2. Supraspinal inhibition —Several supraspinal structures send fibers down the spinal cord to inhibit pain in the dorsal horn. Important sites of origin for these descending pathways include the ***periaqueductal gray, reticular formation, and nucleus raphe magnus (NRM).***

Stimulation of the periaqueductal gray area in the midbrain produces widespread analgesia in humans. Axons from these tracts act presynaptically on primary afferent neurons and postsynaptically on second-order neurons (or interneurons).

These pathways mediate their anti-nociceptive action via ***α2 -adrenergic, serotonergic, and opiate (μ, δ, and κ) receptor mechanisms***. The role of monoamines in pain inhibition explains the analgesic efficacy of antidepressants that block reuptake of catecholamines and serotonin. Inhibitory adrenergic pathways originate primarily from the periaqueductal gray area and the reticular formation. Norepinephrine mediates this action via activation of presynaptic or postsynaptic α2 receptors. At least part of the descending inhibition from the periaqueductal gray is relayed first to the NRM and medullary reticular formation; serotonergic fibers from the NRM then relay the inhibition to dorsal horn neurons via the dorsolateral funiculus.

The endogenous opiate system (primarily the NRM and reticular formation) acts via methionine enkephalin, leucine enkephalin, and β-endorphin, all of which are antagonized by naloxone. These opioids act presynaptically to hyperpolarize primary afferent neurons and inhibit the release of substance P; they also appear to cause some postsynaptic inhibition. Exogenous opioids preferentially act postsynaptically on the second-order neurons or interneurons in the substantia gelatinosa.

Pain Processing

The **four** elements of pain processing include (1) transduction, (2) transmission, (3) modulation, and (4) perception (Fig. 5).

1. **Transduction** is the event whereby noxious thermal, chemical, or mechanical stimuli are converted into an action potential.
2. **Transmission** occurs when the action potential is conducted through the nervous system via the first-, second-, and third-order neurons, which have cell bodies located in the dorsal root ganglion, dorsal horn, and thalamus, respectively.
3. **Modulation** of pain transmission involves altering afferent neural transmission along the pain pathway. The dorsal horn of the spinal cord is the most common site for modulation of the pain pathway, and modulation can involve either inhibition or augmentation of the pain signals.
4. **Perception** of pain is the final common pathway, which results from the integration of painful input into the somatosensory and limbic cortices.

Generally speaking, traditional analgesic therapies have only targeted pain perception. A **multimodal approach** to pain therapy ***should target all four elements*** of the pain processing pathway.

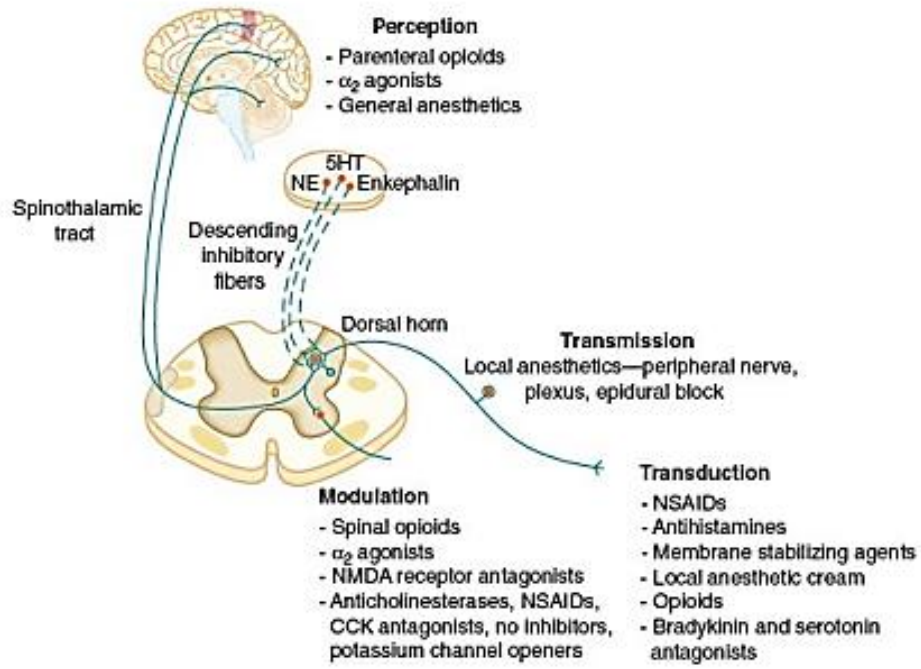


Figure 5. The four elements of pain processing: transduction, transmission, modulation, and perception.

MODULE 4: ACUTE PAIN versus CHRONIC PAIN

Acute pain has been defined as "the normal, predicted, physiologic response to an adverse chemical, thermal, or mechanical stimulus."

It is nearly always nociceptive.

Biological Function

Transient acute pain, as occurs when a person touches a hot stove or steps on a sharp object, promptly alerts the individual and causes him or her to immediately withdraw the limb and thus avoid further damage. Acute pain associated with more severe injuries involving deep somatic structures, such as fractures or sprains, imposes limitation of action and therefore tends to prevent further damage or aggravation of pathophysiology. The protective biological function of acute pain under these circumstances is widely accepted and appreciated. Similarly, acute pain of visceral disease has the biological function of warning the individual that something is wrong, it prompts him or her to consult a physician, and it is used by the physician as an aid in making the diagnosis. Moreover, as previously mentioned, acute pain associated with injury or disease is often associated with certain segmental and supersegmental reflex responses that help the organs maintain homeostasis. These autonomic reflex responses permit a person to ***fight or run*** and later enhance the healing process. In all of these and other circumstances, the pain and the associated reflex responses have an important biological function.

Why do surgeons try to develop minimally invasive surgical techniques?

(ideally, the less trauma to tissues, the less the pain experienced..)

ASK YOURSELF….

Chronic pain is pain that persists beyond the usual course of an acute disease (usually 3 months) or after a reasonable time for healing to occur; this healing period can vary from 1 to 6 months.

Chronic pain may be nociceptive, neuropathic, or mixed. Patients with chronic pain often have attenuated or absent neuroendocrine stress responses and have prominent sleep and affective (mood) disturbances.

When pain becomes chronic, your body's pain signals keep firing for weeks, months, or years, even though the damage that set them off may have long since healed. The pain may have been caused by an injury, and, for unknown reasons, your body never turned off its pain switch. Or the pain may have an ongoing cause, such as arthritis, cancer, or nerve damage. You also may have multiple causes of chronic pain, which is particularly common for older adults.

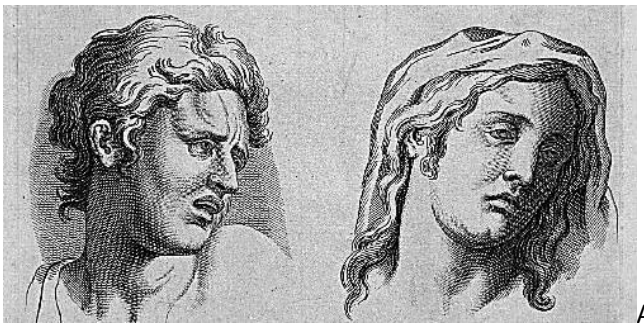
One big difference between acute and chronic pain is when you have acute pain, you usually know why it hurts. (Some examples of acute pain are broken bones, kidney stones, and childbirth.) When you have chronic pain, you may have no idea what's causing the hurting. The bone has healed, the stone has passed, and the baby is now walking and talking, but you still have lingering problems in

the areas where the acute pain occurred. In addition, many people with chronic pain aren't even aware that an injury ever occurred in the first place. (And, indeed, maybe there was no injury to begin with!) For them, the pain appears to slam in from out of the blue, like a sudden tornado that levels a house. Whether you know the source, chronic pain is a sensation without purpose. It has **no biological function**, and its usefulness as a warning system has long since passed or never existed. Ironically, while chronic pain has no purpose, it's still **often difficult to treat**. The medical term for this type of pain is treatment resistant pain.

Experts at the Cleveland Clinic describe chronic pain this way:

It persists, resists, and insists: It persists beyond the expected healing time, resists interventions (treatments), and it also insists upon being recognized.

- As such, ***pain becomes the disease itself.*** It is a malefic force that often imposes severe physical, emotional, economic and social stresses on the patient and on the family.
- Anxiety, depression, and vegetative signs like anorexia, lassitude, sleep disturbance, and decreased libido and often accompany chronic pain.
- Overt pain behaviors (eg, grimacing) and sympathetic hyperactivity are typically absent, patient usually does not appear to be in pain, and the only definitive way to determine the presence of pain is to obtain a verbal report from the patient.



Which of the two is feeling pain?

(Both. The one on the left is typical of acute pain while the one on the right typifies chronic pain behavior.)

ASK YOURSELF….

Pathophysiological changes during the transition of acute to chronic pain (neuroplasticity)

Termination of acute nociception and full tissue recovery would result in restoration of normal homeostasis and end the pain process. However, continuous or repetitive nociceptive stimulation leads to a series of pathophysiological changes in pain processing. Complex changes are observed at all levels from the periphery to the brain resulting in persistent pain.

In the periphery (peripheral sensitization)

Repetitive nociceptive stimulation may result in a prolonged inflammatory process through activation of lymphocytes and release of TNF-a and interleukins such as IL1, IL6, and IL1b. Chronic inflammation leads to a series of changes in the periphery such as:

- reduction of pain threshold in the primary afferent neurones,
- phosphorylation of protein kinases A and C,
- activation of TRPV1 receptors,
- up-regulation of voltage-gated sodium channels and TRPV1 receptors in DRG, and
- increased production of substance P and CGRP in the periphery and the spinal cord.

Within the spinal cord *(*central sensitization)

Continuous nociception stimulation leads to a number of changes in gene and protein expression in both DRG and dorsal horn neurones. The most prominent change is an increase in the mRNA coding for the production of various receptors and ion channels such as Na and TRPV1 receptors. Changes in receptor kinetics lead to the hyperexcitable state of chronic pain.

Another important receptor type in the spinal cord is the **NMDA**. This receptor remains inactive during acute noxious stimulation because of the tightly bound Mg plug. Continuous nociceptive stimulation causes prolonged slow depolarization of the neurones in the dorsal horn. This leads to massive influx of calcium which removes the Mg plug from NMDA receptors allowing glutamate to bind onto NMDA receptors. ***Activation of NMDA receptors leads to the 'wind-up' phenomenon***. Once wind-up has developed, it induces and potentiates a WDR neuronal response to each stimulus. Subsequent sensory stimulation via Ab fibre (touch) ends up with exaggerated WDR neuronal output. Clinically, this manifests as **allodynia**. The end result of the wind-up process is **'neuroplasticity,**' which is a change in neuronal structure with potential enhancement of signal transduction.

Prolonged nociceptive transmission to the spinal cord causes release of neuronal chemokines (fractalkine and monocytic chemotactic protein-1), neurotransmitters (substance P, CGRP, glutamate, and ATP) and neuromodulators (prostaglandins and NO); and produces endogenous danger signals (heat shock proteins and the nuclear protein HMGB1). All these substances activate **glial cells** in the central nervous system.

In the brain

Pain matrix has been identified by radiological evidence. Imagings such as functional magnetic resonance imaging and positron emission tomography scans have identified **five important pain centres** and various changes in the pain matrix when sensitization occurs. The identified regions (and their associated clinical roles) are as follows:

- Thalamus where spinothalamic tract terminates (somatosensory discrimination),
- mid/anterior insula, anterior cingulated cortex and prefrontal cortex (affective and motivational components of pain),

- PAG and RVM (fight-or-flight responses and stress-induced analgesia),
- reticular formation (regulating descending pathways), and
- spinoparabrachial pathway to the hypothalamus and amygdala (autonomic and sensory coordination).

Pathophysiological changes in the pain matrix reflect strong correlation between chronic pain and mental status. Mental issues vary from maladaptive pain coping ability to anxiety and depression. Substance misuse and addiction are not uncommon. Psychological stressors tend to accentuate pain intensity and compromise an individual's ability to cope with pain. Therefore, biopsychosocial evaluation is a critical component of chronic pain management.

Approach to minimize the transition from acute to chronic pain-clinical application of basic science

Physiological changes during the transition of acute to chronic pain are observed at various levels, from the peripheral to the central nervous system. Theoretically, if the pathophysiological changes during this transition **could be prevented or reversed**, we would be able to prevent or minimize the development of chronic pain in practice. Numerous studies have attempted to formulize analgesic approach to prevent this transition, but so far, there has been very limited promising evidence. Apart from ethical and humanitarian reasons, early management of patients with acute pain is paramount in minimizing the risk of chronic pain development. Early recognition of patients with a high risk of developing chronic pain is imperative in reducing chronic pain development. Upon risk stratification, appropriate preventative analgesia aiming at various levels of pain pathways would reduce the potential risk of developing chronic pain.

In theory, reduction of acute pain should reduce central neuroplasticity and minimize the risk of development of chronic pain, yet available evidence is limited.

Preventive Analgesia

Preventive analgesia includes any antinociceptive regimen delivered at any time during the perioperative period that will attenuate pain-induced sensitization. The term *"preventive analgesia" replaces the older terminology "preemptive analgesia,"* which is defined as an analgesic regimen that is administered prior to surgical incision and is more effective at pain relief than the same regimen administered after surgery. Although use of the term preemptive analgesia has been popular in the past, evidence of its clinical benefit in humans has been mixed and the term should be considered obsolete.

The goal of preventive analgesia is to ***block the development of sustained pain***. Theoretically, this occurs by preventing NMDA receptor activation in the dorsal horn that is associated with windup, facilitation, central sensitization expansion of receptive fields, and long-term potentiation, all of which can lead to a chronic pain state.

In order for preventive analgesia to be successful, **three critical principles** must be adhered to:

(1) The depth of analgesia must be adequate enough to block all nociceptive input during surgery,
(2) the analgesic technique must be extensive enough to include the entire surgical field, and
(3)) the duration of analgesia must include both the surgical and postsurgical periods.

Patients with pre-existing chronic pain may not respond as well to these techniques because of preexisting sensitization of the nervous system.

SYSTEMIC RESPONSES TO PAIN

Systemic Responses to Acute Pain

Acute pain is typically associated with a systemic neuroendocrine stress response that is **proportional** to pain intensity. The pain pathways mediating the afferent limb of this response are discussed in module 1. The efferent limb is mediated by the sympathetic nervous and endocrine systems.

Sympathetic activation increases efferent sympathetic tone to all viscera and releases catecholamines from the adrenal medulla. The hormonal response results from increased sympathetic tone and from hypothalamically-mediated reflexes. Moderate to severe acute pain, regardless of site, may adversely affect perioperative morbidity, mortality, and convalescence.

A. Cardiovascular Effects

Cardiovascular effects of acute pain often include hypertension, tachycardia, enhanced myocardial irritability, and increased systemic vascular resistance. Cardiac output increases in most normal patients but may decrease in patients with compromised ventricular function. Because of the increase in myocardial oxygen demand, pain can worsen or precipitate myocardial ischemia.

B. Respiratory Effects

An increase in total body oxygen consumption and carbon dioxide production necessitates a concomitant increase in minute ventilation. The latter increases the work of breathing, particularly in patients with underlying lung disease. Pain due to abdominal or thoracic incisions further compromises pulmonary function because of guarding (splinting). Decreased movement of the chest wall reduces tidal volume and functional residual capacity, promoting atelectasis, intrapulmonary shunting, hypoxemia, and, less commonly, hypoventilation. Reductions in vital capacity impair coughing and clearing of secretions.

C. Gastrointestinal and Urinary Effects

Enhanced sympathetic tone increases sphincter tone and decreases intestinal and urinary bladder motility, promoting ileus and urinary retention. Hypersecretion of gastric acid can promote stress ulceration. Nausea, vomiting, and constipation are common. In addition, systemic opioids used to treat postoperative pain (and also administered as a component of the operative anesthetic) are a common cause of postoperative ileus and urinary retention.

D. Endocrine Effects

Stress increases release of catabolic hormones (catecholamines, cortisol, and glucagon) and inhibits release of anabolic hormones (insulin and testosterone). Patients develop a negative nitrogen balance, carbohydrate intolerance, and increased lipolysis. The increase in cortisol, renin, angiotensin, aldosterone, and antidiuretic hormone results in sodium retention, water retention, and secondary expansion of the extracellular space.

E. Hematological Effects

The neuroendocrine stress response to acute pain may increase platelet adhesiveness, reduce fibrinolysis, and promote a hypercoagulability state.

F. Immune Effects

The neuroendocrine stress response produces leukocytosis and may predispose patients to infection. Worsening carbohydrate intolerance with sustained hyperglycemia also increases the risk of infection. Stress-related immunodepression may enhance tumor growth and metastasis.

G. Psychological Effects

Anxiety and sleep disturbances are common reactions to acute pain. With prolonged duration of the pain, depression is not unusual. Some patients react with frustration and anger that may be directed at family, friends, and the medical staff.

Systemic Responses to Chronic Pain

The neuroendocrine stress response in the setting of chronic pain is generally observed only in patients with severe recurring pain due to peripheral (nociceptive) mechanisms and in patients with prominent central mechanisms such as pain associated with paraplegia. It is attenuated or absent in most patients with chronic pain. Sleep and affective disturbances, particularly depression, are often prominent. Many patients also experience significant decreases or increases in appetite and psychological stress related to social relationships.

MODULE 5. PATHOPHYSIOLOGIC CLASSIFICATION OF PAIN

1. Somatic pain—Somatic pain can be further classified as superficial or deep.

- **Superficial** somatic pain is due to nociceptive input from skin, subcutaneous tissues, and mucous membranes. It is characteristically well-localized and described as a sharp, pricking, throbbing, or burning sensation. It follows dermatomes of segmental nerves.
- **Deep** somatic pain arises from muscles, tendons, joints, or bones. In contrast to superficial somatic pain, it usually has a dull, aching quality and is less well localized. It follows myotomes and sclerotomes.

An additional feature is that both the intensity and duration of the stimulus affect the degree of localization. For example, pain following brief minor trauma to the elbow joint is localized to the elbow, but severe or sustained trauma often causes pain in the whole arm.

2. Visceral pain—Visceral pain is due to a disease process or abnormal function involving an internal organ or its covering (eg, parietal pleura, pericardium, or peritoneum). Visceral structures are highly sensitive to distension (stretch), ischemia and inflammation, but relatively insensitive to other stimuli that normally evoke pain such as cutting or burning.

Visceral pain is diffuse, difficult to localize and often referred to a distant, usually superficial, structure. It may be accompanied by symptoms such as nausea, vomiting, changes in vital signs as well as emotional manifestations. The pain may be described as sickening, deep, squeezing, and dull.

The vague and poorly defined sensation as well as its temporal nature, characteristic of visceral pain, is due to the **low density** of sensory innervation of viscera and the **extensive divergence** of visceral input within the central nervous system (CNS).

- **True visceral pain** is dull, diffuse, and usually midline. It is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating, and changes in blood pressure and heart rate. True visceral pain is characterized as a vague, diffuse, and poorly defined sensation. Regardless of specific organ of origin, the pain is usually perceived in the midline spanning anywhere from the lower abdomen up to the chest. In the early phases the pain is perceived in the same general area and it has a temporal evolution, making the onset sensation insidious and difficult to identify.

- The phenomenon of **visceral or parietal pain referred to cutaneous areas** results from patterns of embryological development and migration of tissues, and the convergence of visceral and somatic afferent input into the central nervous system.

3. Neuropathic pain - is pain caused by damage or disease affecting the somatosensory nervous system. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain.

Neuropathic pain may be associated with abnormal sensations called ***dysesthesia*** or pain from normally non-painful stimuli ***(allodynia***). It may have continuous and/or episodic (paroxysmal) components. The latter resemble stabbings or electric shocks. Common qualities include burning or coldness, "pins and needles" sensations, numbness and itching.

Central neuropathic pain is found in spinal cord injury, multiple sclerosis, and some strokes. Aside from diabetes (diabetic neuropathy) and other metabolic conditions, the common causes of painful **peripheral** neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, remote manifestations of malignancies, immune mediated disorders and physical trauma to a nerve trunk.

Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy), radiation injury or surgery.

Mechanisms

Peripheral

After a peripheral nerve lesion, aberrant regeneration may occur. Neurons become unusually sensitive and develop spontaneously pathological activity and abnormal excitability. This phenomenon is called ***"peripheral sensitization".***

Central

The (spinal cord) dorsal horn neurons give rise to the spinothalamic tract (STT), which constitutes the major ascending nociceptive pathway. As a consequence of spontaneous activity arising in the periphery, STT neurons develop increased background activity, enlarged receptive fields and increased responses to afferent impulses, including normally innocuous tactile stimuli. This phenomenon is called ***central sensitization***. Central sensitization is an important mechanism of persistent neuropathic pain.

Other mechanisms may take place at the central level after peripheral nerve damage.

- The loss of afferent signals induces *functional changes* in dorsal horn neurons.
- A decrease in the large fiber input *decreases the activity of interneurons* inhibiting nociceptive neurons i.e. loss of afferent inhibition.
- *Hypoactivity* of the descending antinociceptive systems or loss of descending inhibition may be another factor.

With the loss of neuronal input (deafferentation) the STT neurons begin to fire spontaneously, a phenomenon designated "***deafferentation hypersensitivity."***

Neuroglia ("glial cells") may play a role in central sensitization. Peripheral nerve injury induces glia to release proinflammatory cytokines and glutamate—which, in turn influence neurons.

Cellular

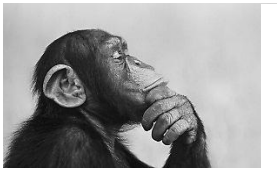
The phenomena described above are dependent on changes at the cellular and molecular levels.

- Altered expression of ion channels, changes in neurotransmitters and their receptors as well as altered gene expression in response to neural input are at play.
- Neuropathic pain is associated with changes in sodium and calcium channel subunit expression resulting in functional changes.
- In chronic nerve injury, there is redistribution and alteration of subunit compositions of sodium and calcium channels resulting in spontaneous firing at ectopic sites along the sensory pathway.

4. PSYCHOGENIC PAIN - is pain in one or more sites that is the predominant focus of clinical attention, which is not ***fully*** accounted for by a non-psychiatric medical or neurological condition. It is associated with emotional distress and functional impairment.

The term "psychogenic pain" is used to describe pain that is believed to be sustained predominantly by psychological factors. It does not refer to the common observation that pain experienced by some patients is exacerbated by psychological factors, or that they have pain-related distress or comorbid psychiatric disease. Rather, psychogenic pain is related to other disorders characterized by prominent somatic symptoms associated with significant distress and impairment.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), by the American Psychiatric Association, classifies a disorder such as this as a "somatic symptom disorder with prominent pain," which is diagnosed on the basis of excessive thoughts, feelings, or behaviors related to pain that are distressing or impair functioning, and appear out of proportion to the physical findings.



"MATSING TYPE"

1. oral mucositis	a. deep somatic
2. gastritis	b. superficial somatic
3. trigeminal neuralgia	c. true localized visceral
4. ankle sprain	d. peripheral neuropathic
5. thalamic pain	e. central neuropathic
6. jaw pain in MI	f. referred visceral
7. pleuritic chest pain	g. localized parietal

ANS: 1.b 2.c 3.d 4.a 5.e 6.f 7.g

MODULE 6: PAIN ASSESSMENT

The evaluation of any patient with pain should include several key components. Information about location, onset, and quality of pain, as well as alleviating and exacerbating factors, should be obtained, along with a pain history that includes previous therapies and changes in symptoms over time. In addition to physical symptoms, chronic pain usually involves a psychological component that should be addressed.

Questionnaires, diagrams, and pain scales are useful tools that help patients adequately describe the characteristics of their pain and how it affects their quality of life. Information gathered during the physical examination can help distinguish pain location, type, and systemic sequelae, if any.

Imaging studies such as plain radiographs, computed tomography (CT), magnetic resonance imaging (MRI), and bone scans can often help delineate physiological causes. All components are necessary for a comprehensive evaluation of the pain patient prior to determining appropriate treatment options.

In taking the pain history, we could use the mnemonic: **OLD CART + ICE:**
O – onset
L – location
D – description/duration
C – characteristic
A – aggravating factors
R – relieving factors
T – therapies tried
I – impact on ADL's
C – coping strategies
E – emotional response

Alternatively, **SOCRATES** can be used:

- **S**ite – Where is the pain? Or the maximal site of the pain.
- **O**nset – When did the pain start, and was it sudden or gradual? Include also whether it is progressive or regressive.
- **C**haracter – What is the pain like? An ache? Stabbing?
- **R**adiation – Does the pain radiate anywhere?
- **A**ssociations – Any other signs or symptoms associated with the pain?
- **T**ime course – Does the pain follow any pattern?
- **E**xacerbating/relieving factors – Does anything change the pain?
- **S**everity – How bad is the pain?

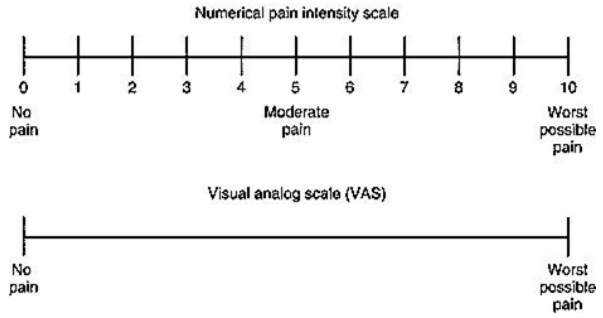
PAIN MEASUREMENT

A reliable measurement of pain severity would help determine therapeutic interventions and evaluate the efficacy of treatments. This is a challenge, however, because pain is a subjective experience that is influenced by psychological, social, cultural, and other variables. Clear definitions are necessary, as pain may be described in terms of tissue destruction or bodily or emotional reaction.

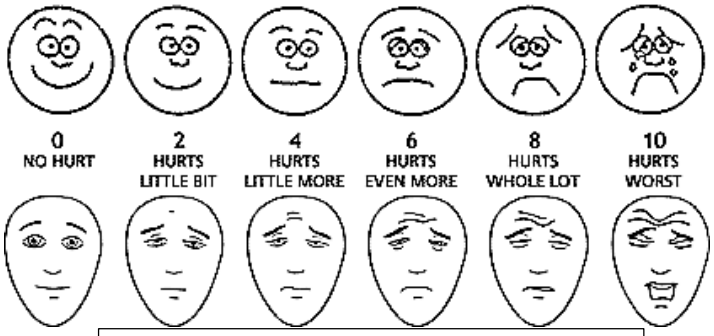
The numerical rating scale, Wong-Baker FACES rating scale, visual analog scale (VAS), and McGill Pain Questionnaire (MPQ) are most commonly used. The **gold standard** of pain assessment is patient's self-reported pain.

- In the **numerical scale,** 0 corresponds to no pain and 10 is intended to reflect the worst possible pain.
- The **Wong-Baker FACES** pain scale, designed for children 3 years of age and older, is useful in patients with whom communication may be difficult. The patient is asked to point to various facial expressions ranging from a smiling face (no pain) to an extremely unhappy one that expresses the worst possible pain.
- The **VAS** is a 10-cm horizontal line labeled “no pain” at one end and “worst pain imaginable” on the other end. The patient is asked to mark on this line where the intensity of the pain lies. The distance from “no pain” to the patient’s mark numerically quantifies the pain. The VAS is a simple and efficient method that correlates well with other reliable methods.
- The **MPQ** is a checklist of words describing symptoms. Unlike other pain rating methods that assume pain is one-dimensional and describe intensity but not quality, the MPQ attempts to define the pain in three major dimensions: (1) sensory–discriminative (nociceptive pathways), (2) motivational–affective (reticular and limbic structures), and (3) cognitive–evaluative (cerebral cortex). It contains 20 sets of descriptive words that are divided into four major groups: 10 sensory, 5 affective, 1 evaluative, and 4 miscellaneous. The patient selects the sets that apply to his or her pain and circles the words in each set that best describe the pain.

PAIN SCALES



Wong-Baker Faces Pain Rating Scale



FACES Pain Scale Revised (FPS-R)

Critical Care Pain Observation Tool (CPOT)

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
OR	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0-8

The Critical Care Pain Observation Tool (CPOT) was designed to assess the pain of critically ill patients who are incapable of reporting their pain.

The FLACC Behavioral Scale

	Scoring		
Categories	0	1	2
Face	No particular expression or smile.	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractable	Difficult to console or comfort

Note: Each of the five categories Face (F), Legs (L), Activity (A), Cry (C), and Consolability (C) is scored from 0-2, which results in a total score between 0 and 10.
From Merkel, Voepel-Lewis, Shayevitz, & Malviya (1997). The FLACC: A behavioral scale for scoring postoperative pain in young children.
Pediatric Nursing, 23 (3) 293-297.

The Face, Legs, Activity, Cry, Consolability scale or **FLACC scale** is a measurement used to assess pain for children between the ages of 2 months and 7 years or individuals that ***are unable to communicate their pain.*** The scale is scored in a range of 0–10 with 0 representing no pain. The scale has five criteria, which are each assigned a score of 0, 1 or 2.

Acute and chronic **neuropathic pain** can be established and measured using validated tools. Examples are as follows:

	LANSS	DN4	NPQ	painDETECT	ID Pain
Symptoms					
Pricking, tingling, pins and needles	x	x	x	x	X
Electric shocks of shooting	X	x	x	x	x
Hot or burning	X	x	x	x	x
Numbness		x	x	x	x
Pain evoked by light touching	X		x	x	x
Painful cold or freezing pain		x	X		
Clinical examination					
Brush allodynia	X	X			
Raised soft touch threshold		X			
Altered pin prick threshold	X	X			

- The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
- The Douleur neuropathique 4 questions (DN4)
- Neuropathic Pain Questionnaire (NPQ)
- The Pain Detect Questionnaire (PD-Q)
- ID Pain in geriatrics

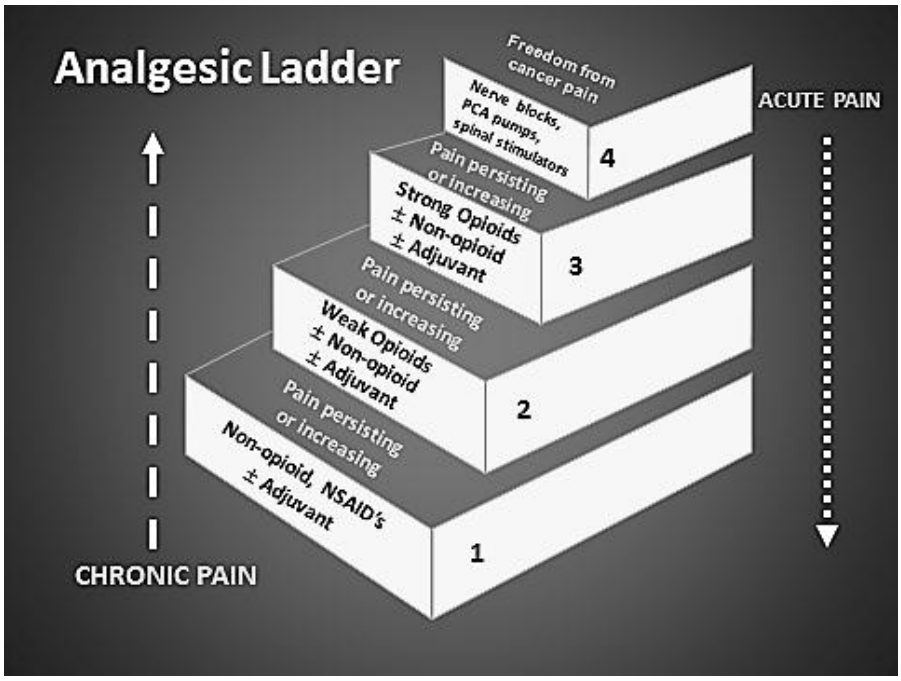
PSYCHOSOCIAL EVALUATION

Psychosocial evaluation is useful whenever medical evaluation fails to reveal an apparent cause for pain, when pain intensity, characteristics, or duration are disproportionate to disease or injury, or when psychological or social issues, or both, are apparent. These types of evaluations help clarify the role of behavioral factors. The most commonly used psychological tests are the Minnesota Multiphasic Personality Inventory (MMPI) and Beck Depression Inventory. The MMPI is used primarily to confirm clinical impressions about the role of psychological factors; it cannot reliably distinguish between "organic" and "functional" pain. Depression is very common in patients with chronic pain. It is often difficult to determine the relative contribution of depression to the suffering associated with pain. The Beck Depression Inventory is a useful test for identifying patients with major depression. Several tests have been developed to assess functional limitations or impairment (disability) and quality of life. These include the Multidimensional Pain Inventory (MPI), Medical Outcomes Survey 36-Item Short Form (SF-36), Pain Disability Index (PDI), and Oswestry Disability Index (ODI).

MODULE 7: PAIN TREATMENT

THE WHO ANALGESIC LADDER

"Pain ladder", or analgesic ladder, was created by the World Health Organization (WHO) as a guideline for the use of drugs in the management of pain. Originally published in 1986 for the management of cancer pain, it is now widely used by medical professionals for the management of all types of pain.



Step 1.	Mild pain:			Non-opioid	+	Optional adjuvant	If pain persists or increases, go to step 2.
Step 2.	Moderate pain:	Weak opioid	+	Non-opioid	+	Optional adjuvant	If pain persists or increases, go to step 3.
Step 3.	Severe pain:	Strong opioid	+	Non-opioid	+	Optional adjuvant	Freedom from pain.

Step 4. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective. More invasive routes of administration (e.g. epidural) may be necessary for a small subset of patients.

Drug selection should be appropriate to the severity of the pain. It may be most appropriate with severe pain to begin at the top of the ladder with a strong opioid; it is not always necessary to start at step one. When pain is controlled, the patient should be maintained on the dose that is effective. It is usually not necessary to step down the ladder unless the cause of pain is believed to have resolved (e.g. post-operatively, in remission from cancer).

Along any step in the ladder, additional drugs – **"adjuvants"-** may be used. The term "adjuvant analgesic" was originally coined to refer to a small number of drugs that were marketed for indications other than pain but were found to be potentially useful as analgesics in patients receiving opioid therapy. Adjuvants include: antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin), corticosteroids (e.g. dexamethasone), and anxiolytics (e.g. diazepam).

The three main principles of the WHO analgesic ladder are:

"By the clock, by the mouth, by the ladder".

By the clock: To maintain freedom from pain, drugs should be given "by the clock" or "around the clock" rather than only "on demand" (i.e. PRN). This means they are given on a regularly scheduled basis. The frequency will depend on whether it is a long- or short-acting preparation.

By the mouth: The oral route is usually the preferred route for ease of use in a variety of care settings. However, it may not be possible for all patients (e.g. end-of-life, unconscious, swallowing issues). When the oral route is not feasible, the least invasive route should be considered (e.g. sub-lingual or sub-cutaneous before intra-venous.). The intra-muscular route should never be used.

By the ladder: If pain occurs in increasing severity as in progressive cancer, there should be prompt administration of drugs in the following order:

1. non-opiods (e. g. acetaminophen, NSAID's) 2. as necessary, mild opiods (e. g. tramadol) 3. then strong opiods (e. g. morphine) until the patient is free of pain.

For acute pain like post-operative pain or during chronic pain with acute breakthrough pain, severe pain is expected at the outset, thus treatment proceeds using the ***down-ladder.***

It is important to understand the limitations of this analgesic ladder approach. Although it is still relevant in providing a framework for the stepwise and systematic approach to managing cancer pain, and describing an appropriate role for opioid therapy, many details are outdated and it should not be viewed as evidence-based or a best practice guideline. For example, the distinction between weak and strong opioids is pharmacologically outmoded and should not be used to justify the selection of one or another drug. Furthermore, at least one contemporary randomized trial found that low-dose morphine (up to 30 mg daily) reduced pain significantly as compared to codeine (or tramadol) with or without acetaminophen in patients with moderate cancer pain with similar tolerability and an earlier effect.

The decades since the publication of the analgesic ladder have also witnessed the development of many **other options for pain control**, which are outlined in the table below.

Multimodal analgesia combines two or more drugs to address the pain. In this way, there is reduced doses of each analgesic, improved antinociception due to synergistic/additive effects, and reduced severity of side effects of each drug. **Pharmacologic, Interventional, and non-pharmacologic approaches (physical/psychologic)** to pain management are usually combined for optimum results.

Categories of treatment for pain in cancer patients

Pharmacological
Opioid analgesics
Non-opioid analgesics
Non-traditional analgesics (adjuvant analgesics)
Interventional
Injection therapies
Neural blockade
Implant therapy
Rehabilitative
Therapeutic exercise
Occupational therapy
Hydrotherapy
Treatment for specific disorders (eg, lymphedema)
Psychological
Psychoeducational interventions
Cognitive behavioral therapy
Relaxation therapy, guided imagery, other types of stress management
Other forms of psychotherapy
Neurostimulation
Transcutaneous
Transcranial
Implanted
Integrative (complementary or alternative)
Acupuncture
Massage
Physical or movement
Others

Reproduced from: Portenoy RK. Treatment of cancer pain. Lancet 2011; 377:2236.

I. ACETAMINOPHEN/PARACETAMOL

ACETAMINOPHEN has been used alone for mild pain. It is also a component of a variety of combination opioid products (acetaminophen plus tramadol, codeine, hydrocodone, or oxycodone). When used in combination with an opioid to treat postoperative pain, acetaminophen has an ***opioid-sparing effect***.

The analgesic mechanisms underlying the benefit of acetaminophen are poorly understood, but may involve ***inhibition of prostaglandin formation in the CNS***, as well as other mechanisms. In contrast to the NSAIDs, acetaminophen is not anti-inflammatory, at least when peroxidase levels are high (eg, with tissue damage, and/or inflammation in peripheral sites).

Intravenous acetaminophen — Intravenous (IV) has a more rapid and predictable onset of effect (5 to 10 minutes) and time to peak concentration (15 minutes) in most patients compared with rectal or

oral administration (onset 10 to ≥60 minutes). The usual dose of IV acetaminophen for patients over 50 kg is 650 mg every four hours or 1000 mg every six hours, ***not to exceed 4 g per day***.

A reduced dose of acetaminophen should be used for low-weight adults (body weight 33 to 50 kg) and in patients with mild or moderate hepatic insufficiency, chronic alcoholism, malnutrition, or dehydration. Patients with severe renal insufficiency (creatinine clearance ≤30 mL/min) may receive the usual dose, but not more often than once every six hours. Acetaminophen is contraindicated in patients with severe hepatic insufficiency or severe progressive liver disease.

Health care providers should only prescribe **combination products** that contain *325 mg or less of acetaminophen per dosage unit.* The maximum dose should be limited to 4 g/day with maximal single doses not to exceed 1000 mg. The maximum daily dose should be lower, eg, a maximum of 3 g/day, if a patient has known liver disease (including liver metastases).

Patients taking combination drug products that contain acetaminophen must be educated to limit alcohol consumption while taking acetaminophen and to avoid unintentional overdose

II. NONSTEROIDAL ANTIINFLAMMATORY AGENTS

The NSAIDS are a diverse group of drugs that presumably produce analgesia by inhibiting the enzyme cyclooxygenase (COX), and thereby reducing production of peripheral and central prostaglandins. There are two main isoforms of COX, a ***constitutive form (COX-1)*** that is active in tissues that require prostaglandins for physiologic function, and ***an inducible form (COX-2)*** that is produced in the setting of inflammation.

Each of the NSAIDs inhibits both COX-1 and COX-2, but with varying selectively for the two isoforms. Drugs that are relatively more selective for COX-2 have analgesic and anti-inflammatory properties, but are relatively less likely to produce side effects related to COX-1 inhibition, such as gastrointestinal (GI) toxicity.

NSAIDS are effective analgesics for cancer pain when used as single agents or in combination with opioids. Based upon clinical observations, NSAIDs may be especially useful in patients ***with bone pain or pain that is related to grossly inflammatory lesions***. They are relatively less useful in patients who have neuropathic pain. However, the utility of NSAIDs for cancer pain is limited by side effects and a ***"ceiling" dose for analgesia***, above which additional dose increments fail to produce more relief.

Side effects — Side effects that may be associated with NSAIDs include the following:

Cardiovascular toxicity — The mechanism by which nonsteroidal antiinflammatory drugs (NSAIDs) lead to an increase in cardiovascular events, such as myocardial ischemia and stroke, is likely related to their impact on inhibition of cyclooxygenase (COX)-2, which is associated with reduced prostaglandin I2 (PGI2 or prostacyclin) production by vascular endothelium with little or no inhibition of potentially pro-thrombotic platelet thromboxane A2 production. ***The relatively selective reduction in prostacyclin activity could predispose to endothelial injury.***

Gastrointestinal toxicity — NSAIDs produce both dyspepsia and gastroduodenal ulceration (peptic ulcer disease). The likelihood and severity seem to be less with COX-2-selective drugs than with ibuprofen and naproxen, at least over the short-term.

Nephrotoxicity — Reversible renal insufficiency due to renal vasoconstriction, acute interstitial nephritis, and a predisposition to acute tubular necrosis in patients with low renal perfusion have been associated with NSAID use. Prolonged NSAID use also can cause chronic nephropathy, which may be irreversible.

Hepatotoxicity — Hepatotoxicity can be seen with NSAIDs, even at recommended doses. The elevations in liver enzymes are generally mild and reversible with discontinuation of the NSAID.

Indications and contraindications — A trial of a NSAID may be considered in any patient who has mild to moderate chronic cancer pain. However, the decision to offer treatment should consider the likelihood of benefit, the risk of adverse effects, and the cost and burden associated with prolonged treatment.

Pharmacologic approaches to preventing gastroduodenal toxicity include the concurrent use of a gastroprotectant (eg, a proton pump inhibitor [PPI] such as omeprazole, or the prostaglandin analogue misoprostol). A PPI is preferred over other preventive approaches because of their convenience and relatively good safety profile.

Regardless of the agent chosen, all patients receiving an NSAID should be evaluated periodically for occult fecal blood, changes in blood pressure, and effects on renal or hepatic function.

III. OPIOIDS

Opioids are widely used for treatment of pain in patients with cancer because of their safety, multiple routes of administration, ease of titration, reliability, and effectiveness for all types of pain (ie, somatic, visceral, neuropathic). Although neuropathic pain may be more difficult to treat, a favorable response to opioid-based analgesia is often possible.

Mechanism of action — Opioids act by binding to specific receptors, the best characterized of which are the **mu, kappa, and delta receptors**. These receptors are present in tissues throughout the body, including both the peripheral and central nervous systems.

Based upon their effects on the mu receptor, opioids are conventionally divided into pure agonists, agonist-antagonists (of which there are two subtypes: partial agonists and mixed agonist-antagonists), and pure antagonists. Mu receptor antagonists have no intrinsic analgesic properties; they are used to prevent or reverse opioid effects.

1. Pure mu agonists

A. Morphine — Morphine is the prototype opioid drug for moderate to severe cancer pain on the third step of the WHO analgesic ladder. It is usually considered to be a standard for comparison. It has a variable oral bioavailability, between 10 and 45%. Morphine has a short half-life, but it is available in multiple formulations, including immediate-release tablets, oral liquid, suppository, solution for intravenous (IV) and subcutaneous (SC) use, and modified-release drugs that provide continuous analgesia with once or twice daily dosing. The short half-life formulations are preferred by some patients and also may be useful for breakthrough pain when co-administered with a long-acting formulation.

- Regardless of the formulation, morphine is primarily ***metabolized in the liver and its metabolites are renally excreted***. Two active metabolites have been extensively studied, morphine-3-glucuronide (M3G) and morphine-6-gluconoride (M6G). Preclinical data and limited human studies suggest that M6G contributes to analgesic activity and M3G may be the cause of some of the side effects that occur during morphine therapy, although this is not yet proven.

Metabolite concentration may be idiosyncratically high as a result of unknown but presumed genetic factors, or more commonly, metabolite concentration may increase relative to the parent compound (morphine) as a result of renal disease that reduces excretion of both glucuronides. If this occurs, use of the drug may be associated with unanticipated potency or side effects.

Clinically, this means that morphine *should be administered cautiously* in the setting of renal insufficiency, and if fluctuation in kidney function can be anticipated, morphine may not be the preferred opioid given the risk of changes in effects and side effects as metabolite accumulation occurs.

Common side effects of morphine include dry mouth, sedation, constipation, nausea, pruritus, and myoclonus. These should be addressed as they may be as disconcerting as the pain itself.

Accordingly, morphine should not be considered the “drug of choice,” but rather, just one of many drugs that could be selected for chronic cancer pain. The decision to select one or another is often based upon the experience of the clinician, prior experience of the patient, cost, dosing implications of the formulation, and other factors.

RECOMMENDATIONS FOR USE OF MORPHINE FOR CANCER PAIN

(by the ***Expert Working Group of the European Association for Palliative Care***)

1. The optimal route of administration is by mouth. Ideally, 2 types of formulation are required:
    - Immediate release – for dose titration
    - Controlled release – for maintenance treatment
2. The simplest method of dose titration is with a dose of immediate release morphine given every 4 hours and the same dose for breakthrough pain. This rescue dose may be given as often as required (for example, every hour), and the total daily dose of morphine can be reviewed daily. The regular dose can then be adjusted according to how many rescue doses have been given.
    - There is no such thing as a standard dose of morphine.
    - The dose must be titrated against effect for each patient.
    - The starting dose will be determined by previous analgesic treatment.
    - Patients changing from a weak opioid will usually start with 10 mg every 4 hours.
    - If step 2 of the analgesic ladder is omitted, 5 mg every 4 hours may suffice.
    - Patients converted from another strong opioid may require more.
    - During dose titration it is preferable to use a formulation of morphine that has a rapid onset, a predictable effect, and a short duration of action to allow steady state to be achieved as quickly as possible.
    - Peak plasma concentrations usually occur within the first hour of oral administration of immediate release morphine, and analgesia lasts for about 4 hours.
    - In contrast, controlled release morphine tablets produce delayed peak plasma concentrations after 2 to 4 hours, and analgesia lasts for 12 hours.
    - The plasma elimination half-life of morphine is 2 to 4 hours, and steady state is reached within 4 to 5 half-lives (that is, within 24 hours) after the start of treatment and every dose adjustment.
    - Various fractions of the regular dose have been recommended for treating breakthrough pain, but there is no logic to using a smaller rescue dose.
    - The full dose is more likely to be effective, and any dose related adverse effects will be insignificant.
    - Patients stabilized on a four hourly regimen should continue to use the same dose for breakthrough pain.

- For patients maintained on a 12 hourly regimen of controlled release morphine, the appropriate rescue dose of an immediate formulation will be 1/3 of the regular dose (that is, equivalent to the 4 hourly dose of morphine).

Table 1. *Time (hours) to peak plasma concentration, elimination half-life, and duration of analgesia after single doses of immediate release and controlled release morphine formulations in patients with normal renal and hepatic function*

	Formulation	
	Immediate release	Controlled release
Time to peak plasma conc.	0.25-1.0	2-4
Elimination half- life	2-4	2-4
Duration of analgesia	4	12

3. If pain returns consistently before the next regular dose is due, the regular dose should be increased. In general, immediate release morphine does not need to be given more often than every four hours and controlled release morphine more often than every 12 hours.
    - It is important to keep the drug regimen as simple as possible.
    - There is no advantage in increasing the frequency of administration and a considerable disadvantage to the patient in terms of convenience and compliance.
4. Several countries do not have an immediate release formulation of morphine (though such a formulation is necessary for optimal management). A different strategy is needed if treatment is started with controlled release morphine.
5. For patients receiving immediate release morphine every four hours, a double dose at bedtime is a simple and effective way of avoiding being woken by pain.
6. Administration of controlled release morphine every eight hours may be occasionally necessary or preferred.
7. Several controlled release formulations are available. There is no evidence that they are substantially different in their duration of effect and relative analgesic potency.
8. If patients are unable to take drugs orally, the preferred routes are rectal and subcutaneous.

9. The bioavailability of morphine by rectal and oral routes is the same, and the duration of analgesia is also the same.

10. The relative potency ratio of oral morphine to rectal morphine is 1 : 1.

11. Controlled release morphine tablets should not be crushed or used for rectal or vaginal administration.

12. Morphine may be given subcutaneously either as bolus injections every four hours or by continous infusion.

13. The relative potency of oral morphine to subcutaneous morphine is about 1 : 2.

14. There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful.

15. Other opioids may be preferred to morphine for parenteral use because of their greater solubility: diamorphine in Britain and hydromorphone elsewhere.

16. Subcutaneous administration of morphine may not be practical in patients

    a. With generalized edema

    b. Who develop erythema, soreness, or sterile abscesses with subcutaneous administration

    c. With coagulation disorders

    d. With very poor peripheral circulation

In these patients, intravenous administration is preferred. Intravenous administration may also be the best parenteral route in patients who, for other reasons, have an indwelling central line or peripheral line.

17. The relative potency ratio of oral to intravenous morphine is about 1 : 3.

18. The above guidelines produce effective control of chronic cancer pain in about 80% of patients. In the remaining 20% other methods of pain control must be considered, including spinal administration of opioid analgesics alone or in combination with local anesthetics or other drugs. There is insufficient evidence to allow recommendations about precise indications for these routes of administration.

19. The buccal, sublingual, and nebulized routes of administration of morphine are not recommended because presently there is no evidence of clinical advantage over conventional routes.

20. Sublingual or transdermal use of other opioids may be an alternative to subcutaneous injection.

B. Oxycodone is a semisynthetic derivative of thebaine. It has intrinsic analgesic properties (activation of kappa-opioid receptors) and predominantly a prodrug. It is converted by the enzyme cytochrome P450 2D6 to oxymorphone (a mu-opioid agonist) and noroxycodone, an inactive metabolite. Compared to morphine, it has a ***higher bioavailability (60%),*** does not have the metabolic issues, and appears to be associated with a lower incidence of hallucinations and itching. The oxycodone:morphine ratio is 1:1.5. It's NNT of 2.5 in neuropathic pain is comparable to antidepressants. The controlled-release preparation (Oxycontin) has ideal analgesic characteristics but there have been numerous reports of abuse from people crushing the preparation and either inhaling the powder or injecting a solution of the drug into their veins

C. Hydromorphone is highly soluble in water and a commercially available concentrated solution (10 mg/mL) facilitates SC or IV administration of relatively high doses. Some clinicians prefer to use hydromorphone in patients with renal insufficiency because its active, renally-cleared metabolites appear in relatively low concentration (compared with morphine) and may be unlikely to cause unanticipated effects. It is a mu-receptor agonist, is ***3 to 5 times more potent than morphine*** orally and 5 to 7 times as potent parenterally. Its duration of analgesic effect, at 3-4 hours, is similar to morphine. Pruritus, sedation, nausea and vomiting occur less frequently compared to morphine. Its metabolite, hydromorphone-3-glucoronide (H3G) lacks analgesic property but possesses neuroexcitatory properties similar to M3G.

D. Oxymorphone - The analgesic efficacy of oxymorphone is comparable to other opioids. It has a relatively low propensity to release histamine, a characteristic also shared with fentanyl. At least in theory, this may reduce the risk of pruritus or urticaria, although there is no evidence that this difference is clinically relevant.

E. Hydrocodone - Short-acting hydrocodone is only available in the United States in combination with acetaminophen. The amount of the nonopioid constituent limits use of these short-acting combinations to relatively opioid-naive patients with moderate pain.

F. Fentanyl — Fentanyl is a highly lipophilic opioid that may be used parenterally or in formulations developed *for transdermal or oral transmucosal* delivery. The transdermal formulation is used for chronic pain. Both the non-oral route and the relatively infrequent dosing (every two to three days for transdermal fentanyl) are considered advantages by some patients. Although data from clinical trials about the potential for a relatively reduced risk of constipation from transdermal fentanyl are conflicting, three meta-analyses have found a significant advantage for transdermal fentanyl over sustained release oral morphine in terms of this side effect. *Fentanyl may be preferred over morphine in patients with renal insufficiency due to lack of active metabolites.*

Exposing the patch to heat (eg, an increase in body temperature, use of a heating pad or warming blanket during surgery) may cause an unintentional increase in systemic fentanyl absorption, which may increase the risk of respiratory depression. In addition, fentanyl patches contain metal, which can pose a risk for local skin burn during magnetic resonance imaging (MRI). Physicians should advise

patients to remove the patch before an MRI procedure and replace it after completion of the scan. Rapid onset transmucosal preparations of fentanyl are discussed below.

G. Methadone — Methadone is a mu agonist opioid, but it has a unique pharmacology that presumably underlies both the observation that some patients experience a surprising degree of analgesia after being switched to a relatively low dose and the fact that others experience unanticipated toxicity. At least one controlled trial has shown that methadone is equally effective to morphine for cancer pain. Among the potential benefits of methadone use are its ***low cost*** and ***long duration of action***; it is the only long acting opioid available in a liquid formulation. Because only approximately 20 percent of a dose is eliminated unchanged by the kidneys and there are ***no active metabolites***, methadone, when dosed appropriately, also may be a useful drug in patients with kidney disease.

The fact that methadone is ***effective in treating the opioid craving*** that occurs in those with opioid addiction has been used as a rationale for the use of this drug in those patients who develop aberrant drug-related behavior when given another mu agonist for cancer pain and for those who are a high risk of these behaviors before starting therapy.

Methadone has ***a variable half-life***, which averages approximately 24 hours but ranges from 12 hours to almost one week. Since five to six half-lives are required before steady state plasma concentrations are approached, the time required before a methadone regimen can be considered stable varies from several days to several weeks. During the period when plasma levels are rising toward steady state levels, the patient must be considered at risk for unintentional overdose from accumulation in plasma.

Due to highly variable and prolonged terminal half-life, methadone has the highest risk of among opioids of accumulation and ***overdosage*** during initial titration to effect, and during dose adjustment in chronic use.

H. Codeine is transformed to morphine, via the enzyme cytochrome P450 2D6, and has an NNT of 16.7. Some (9%) of white people do not have the enzyme and do not experience analgesia from codeine. It was conventionally considered to be a first-line agent for the treatment of mild to moderate pain in patients with limited opioid exposure. Codeine is also available in combination with acetaminophen.

I. Meperidine is not preferred for use in the cancer pain population. It is metabolized into a compound (normeperidine) that is relatively toxic, and associated with tremulousness, delirium and seizures. Accumulation of the metabolite is most likely to occur during repeated administration, and dose escalation, and in the setting of impaired elimination caused by renal insufficiency. It is safer to select an alternative mu agonist for the management of chronic pain. It has numerous undesirable side effects including additional anticholinergic effects, high lipophilicity which induces drug-seeking behavior, and its metabolite normeperidine is a CNS stimulant. It is 8-10 times less potent than morphine, has a poor and variable oral absorption, and a short duration of action (2-3 hours).

2. Mixed agonist-antagonist drugs — Drugs of the mixed agonist-antagonist group (***butorphanol, dezocine, pentazocine and nalbuphine)*** are generally not preferred for cancer pain management. This is because of a ceiling effect for analgesia, and the capacity to induce abstinence when administered to patients already receiving other opioids of the mu agonist class.

3. Mixed mechanism drugs: Tramadol and tapentadol — ***Tramadol and tapentadol*** are centrally acting analgesics whose mode of action is based both on the mu receptor binding and monoamine (serotonin and norepinephrine) reuptake blockade. Tramadol is widely used in some countries for moderate to severe cancer pain as an alternative to other opioids, but it is not used as commonly in the United States.

Tramadol is an opioid agonist and a monoaminergic drug. It has a high bioavailability (80-90%) and a dose dependent analgesic efficacy with NNTs of 8.5 for 50 mg, 5.3 for 75 mg, 4.8 for 100 mg, and 2.9 for 150 mg. Maximum dose is **600 mg per day**. The risk of fatal respiratory depression is minimal and possibly limited to patients with severe renal failure, it has a low abuse potential, and the incidence and severity of constipation is less.

In patients taking opioids the following should be distinguished from each other:

A. PHYSICAL DEPENDENCE

- involves the development of a withdrawal syndrome following abrupt discontinuation of therapy or substantial dose reduction.
- Symptoms of withdrawal may include agitation, insomnia, diarrhea, sweating, and rapid heartbeat.
- It is a normal and expected response to continuous opioid therapy.
- It may occur within a few days of dosing with opioids, although it varies among patients.
- It does not mean that the patient is addicted.
- Patients whose pain has been relieved by surgical or other means should have their opioid analgesics reduced by 15-25% every 2 days.

B. TOLERANCE

- is defined as the requirement for dose escalation to maintain the same drug-related effect.
- is a normal physiologic response to chronic opioid therapy.
- is not related to the development of addiction.
- Fear of tolerance does not justify a decision to withhold or delay a therapeutic opioid trial.

Tolerance to Analgesia

- Patients with unchanging pain can have a consistent level of pain relief from the same dose of morphine over time. This is in contrast to the rapid development of tolerance seen in intravenous drug users without pain.
- The need for higher doses of morphine in cancer pain is typically due to disease progression thus worsening pain, rather than tolerance.

Tolerance to Opioid Side Effects

- is a positive phenomenon that often allows upward titration to satisfactory pain relief.
- develops in a few days from use.
- almost never develops to constipation.

C. ADDICTION

- is compulsive use of drugs for non-medical reasons.
- is characterized by a craving for mood altering drug effects, not pain relief.
- means aberrant, dysfunctional changes in behaviour, in sharp contrast to the improved function and quality of life that result from pain relief.
- is extremely rare in cancer patients who use opioids for pain.
- ***Pseudoaddiction*** is a term that describes the development of aberrant behaviour in cancer patients who are experiencing unrelieved pain. When pain is relieved, the behaviors cease and opioids are used responsibly.

IV. ADJUVANT ANALGESICS The term "adjuvant analgesic" was originally coined to refer to a small number of drugs that were marketed for indications other than pain but were found to be potentially useful as analgesics in patients receiving opioid therapy. The term is used interchangeably with the term ***"co-analgesic"*** and can be used to denote any drug with a major clinical use other than pain that is used as an analgesic in selected circumstances.

ADJUVANT ANALGESICS				
Antidepressants	Tricyclics (amitriptyline, nortriptyline, desipramine) SNRI (Duloxetine)	Modulation of neurotransmission of serotonin and norepinephrine	Sedation, tachycardia, urinary hesitancy, weight gain	25–150 mg HS 20–90 mg/d
Antiepileptics	Gabapentin Pregabalin Lamotrigine Carbamazepine	$\alpha_2\delta$ subunit of voltage-gated N-type Ca^{2+} channel modulation Na^+ channel blocker Na^+ channel blockade	Drowsiness, confusion, weight gain, rash LFT monitoring for carbamazepine	300–3600 mg/d 75–600 mg/d 100–600 mg/d 200–1200 mg/d
Muscle relaxants	Baclofen Cyclobenzaprine Methocarbamol	Selective GABA-b agonist Unknown action on CNS	Confusion, drowsiness, dizziness	10–80 mg/d 2–32 mg/d 10–60 mg/d 500–2000 mg/d
Alpha-2 adrenergics	Clonidine Tizanidine	α_2 adrenergic agonism	Drowsiness, ↓BP, ↓HR LFT caution – tizanidine	01–0.3 TD patch 2–32 mg/d
NMDA blockers	Ketamine	NMDA blockade	Delerium, ↑BP, ↑HR, cognition, hepatotoxicity, vesicopathy	10–240 mg/d PO 50–600 mg/d SC
Local anesthetic	Mexelitine	Na^+ channel blocker	Liver toxicity, ↓BP	150–900 mg/d
Corticosteroids	Methyl prednisone Dexamethasone		Hyperglycemia, weight gain, edema, agitation	Variable 4–96 mg/d

Available agents — The large and growing number of adjuvant analgesics can be categorized as:

- Drugs potentially useful for any type of pain (multipurpose analgesics)
- Drugs used for treatment of neuropathic pain
- Drugs used for bone pain
- Drugs used for pain and other symptoms in the setting of bowel obstruction

A. MULTIPURPOSE ANALGESICS FOR ANY TYPE OF CHRONIC PAIN

1. Glucocorticoids — Glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure.

Dexamethasone

- is usually preferred for the management of cancer-related pain, presumably because of its long half-life and relatively low mineralocorticoid effects. However, there is no empiric evidence that this drug is either safer or more effective in the cancer population than any other glucocorticoid. Prednisone and methylprednisolone are acceptable alternatives.

- A typical regimen for patients with cancer-related pain is ***1 to 2 mg*** of dexamethasone orally or parenterally twice daily; this may be preceded by a larger loading dose of 10 to 20 mg.

- Regardless of the regimen that is selected, the intent is usually for ongoing chronic use in the setting of advanced illness. In this situation, the risk of long-term toxicity, which includes myopathy, immunocompromise, psychotomimetic effects, and hypoadrenalism, is attenuated by the limited life expectancy and the need to address the multiple sources of suffering.

- There are some situations for which a brief regimen of high-dose glucocorticoids might be selected. Originally developed for the treatment of emerging epidural spinal cord compression (including ***cauda equina syndrome***), a brief period of high-dose glucocorticoids may be considered for any "pain crisis," which is defined as severe and escalating pain that is not responding sufficiently to an opioid. In such cases, a typical regimen consists of a dexamethasone **loading dose of 50 to 100 mg intravenously**, which may be followed by 12 to 24 mg four times daily; this dose is then tapered over one to three weeks.

2. Analgesic antidepressants — For a patient with chronic cancer pain that is poorly responsive to opioid therapy who also has a depressed mood, we suggest an early trial of an analgesic antidepressant.

Preferred options include:

- serotonin-norepinephrine reuptake inhibitor (SNRI), ***such as duloxetine***
- The tricyclic antidepressants include tertiary amines, ***such as amitriptyline*** or a secondary tricyclic drug***, such as desipramine.***

Mechanism of analgesic effect — Antidepressants function as primary analgesics. Although pain reduction may be enhanced if there is a positive mood effect, ***analgesia is not dependent on mood elevation,*** and pain can be improved in euthymic patients. If a patient with chronic cancer pain has a depressed mood, a relatively early trial of an analgesic antidepressant is appropriate in the hope of achieving a separate and positive effect on mood.

The primary analgesic mode of action is thought to be related to the enhanced availability of monoamines at synapses within neural pathways that are part of the descending pain modulating system. *Inhibition of norepinephrine reuptake appears to be the most important mode of action, but serotonergic and dopaminergic effects also may play a role in analgesia.*

3. Alpha-2 adrenergic agonists - Although the mechanism of the analgesic effects produced by alpha-2 adrenergic agonists is unknown, they presumably relate to increased activity in monoamine-dependent endogenous pain modulating pathways in the spinal cord and brain.

- **Clonidine**, which can be administered orally, transdermally, or intraspinally, has been mainly studied in patients with non-cancer-related chronic pain. Spinally administered clonidine has analgesic properties in patients with cancer pain and is more efficacious for neuropathic than nociceptive pain.
- There is less evidence of analgesic efficacy with **tizanidine**, an orally active centrally acting alpha-2 agonist that is approved as an antispasticity agent, or the parenteral alpha-2 agonist **dexmedetomidine.**

4. Topical therapies — The most widely used topical therapies for pain contain local anesthetics.

- **Lidocaine** —Lidocaine 5 percent patches are widely used for treatment of focal and/or regional pain of all types; lidocaine gels and creams are less widely used because they have to be reapplied two to four times per day, but they are less expensive
- **Capsaicin** — Capsaicin, a naturally occurring constituent of the chili pepper, depletes substance P from the terminals of afferent C fibers. Topical application of a commercially available 0.075 percent capsaicin cream or low-dose transdermal patch (which are available over the counter in the United States) has yielded weak to moderate analgesic effects

B. DRUGS FOR NEUROPATHIC PAIN

Neuropathic pain may be caused by the cancer (eg, radiculopathy from local tumor invasion) or the antineoplastic treatment (eg, chemotherapy-related neuropathy).

- If neuropathic pain is associated with a significant depressed mood, we suggest first-line therapy with an antidepressant. Preferred options include a serotonin-norepinephrine reuptake inhibitor (SNRI), beginning with duloxetine. If duloxetine is not tolerated or available, a trial of an alternative SNRI, such as milnacipran, should be considered before a trial of a secondary tricyclic drug, such as desipramine.

- For patients with neuropathic pain that is not associated with a depressed mood, we suggest first-line therapy with **gabapentin or pregabalin**. We generally prefer pregabalin because of the simplified dosing.

1. Gabapentin and pregabalin — The gabapentinoids gabapentin and pregabalin both act *by binding to the alpha-2-delta protein modulator of the N-type voltage-gated calcium channel*. Binding to this protein reduces calcium influx into the neuron and lessens the likelihood of depolarization. Unlike all other anticonvulsants, gabapentin and pregabalin are **not** metabolized in the liver, and they have few drug-drug interactions, with the exception of enhancing the central nervous system (CNS) depressive effects of CNS depressants. The possibility of serious adverse consequences from this type of interaction may exist when a gabapentinoid and an opioid are co-administered. Two population-based, nested case-control studies employed multivariable analyses and revealed that the combination of an opioid plus either pregabalin or gabapentin was associated with an increased risk of mortality. These findings suggest that *gabapentinoids should be administered cautiously to patients who are receiving centrally acting drugs with sedative effects, especially opioid drugs.*

Both drugs are excreted by the kidneys, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness, and somnolence; edema and weight gain are less common.

Both gabapentin and pregabalin have been extensively studied for diverse types of neuropathic pain, particularly postherpetic neuralgia and painful diabetic neuropathy.

We generally prefer pregabalin because of the simplified dosing:

- A typical starting dose of pregabalin is 50 to 75 mg per day, increased to 100 to 150 mg per day in two divided doses after a few days. Further escalation to the usual effective dose of 150 to 300 mg twice daily typically is accomplished in two to three steps over one to two weeks. In medically frail cancer patients and those with significantly impaired kidney function, the starting dose should be reduced to 25 mg per day, and titration is slower.

- Gabapentin is often initiated at a dose of 300 mg per day (or 100 mg per day in the medically frail or renally impaired). The dose is doubled and administered as two divided doses per day

after a few days. The dose is then gradually escalated every few days while monitoring analgesia and side effects. If pain relief does not occur, in the absence of an analgesic ceiling (dose escalation does not yield more analgesia) and adverse effects, escalation can extend to 3600 mg per day, administered in two to three divided doses. Occasional patients benefit from even higher doses. If possible, it is preferable to taper these drugs prior to discontinuation.

2. Other anticonvulsants — Other anticonvulsants, such as ***carbamazepine, oxcarbazepine, valproate, topiramate, or lacosamide,*** may be effective in some patients, but they are all associated with more side effects and lower efficacy rates than the gabapentinoids. Thus, they should only be considered in a trial in patients who are intolerant of or who experience pain that is unresponsive to gabapentinoids and other adjuvant analgesics, such as antidepressants. There is no evidence as to which patients should have which drug and in which order the drugs should be used.

3. Ketamine and other NMDA receptor antagonists — The N-methyl-D-aspartate (NMDA) receptor is involved in both the sensitization of central neurons and the functioning of the opioid receptor, and there is evidence that one of the commercially available NMDA receptor antagonists, ketamine, has analgesic properties. Many experts believe that ketamine at subanesthetic doses may be useful as a brief infusion for treatment of severe refractory pain, or as a more prolonged infusion or oral therapy in the context of refractory pain associated with advanced illness

Nevertheless, use of intravenous ketamine for chronic pain is supported in consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists, and ketamine continues to be used by specialists in palliative medicine to address refractory pain at the end of life. The side effect profile of ketamine, particularly psychotomimetic effects (including hallucinations and delirium), can be problematic, and as a result, the most common use is for short-term therapy in a monitored setting. Based upon anecdotal observations that treatment with a benzodiazepine, such as lorazepam, or a neuroleptic, such as haloperidol, reduces the risk of psychotomimetic effects from ketamine, most practitioners co-administer one of these drugs prior to the start of the infusion and repeatedly during longer-term treatment. Gradual dose titration of ketamine may also reduce the incidence of psychotomimetic effects.

Other NMDA receptor antagonists, such as **memantine, amantadine, and dextromethorphan**, have been studied in neuropathic pain states, with mixed results. They are rarely considered for trials in cancer-related neuropathic pain that has not responded to other agents.

4. GABA receptor inhibitors and agonists — Among the gamma-aminobutyric acid (GABA) receptor inhibitors are the **benzodiazepines**, which affect the GABAA receptor subtype, and baclofen, which affects the GABAB receptor subtype. As noted previously, the only benzodiazepine that is used for neuropathic pain is **clonazepam**, and this use is based on anecdotal observations.

Baclofen, a selective GABAB agonist, is an ***antispasticity*** drug with established efficacy in trigeminal neuralgia. It has been used anecdotally for neuropathic pain of other types, including cancer pain. A low starting dose of 5 mg twice daily can be gradually escalated to doses that may exceed 200 mg per day in some patients.

C. DRUGS FOR BONE PAIN

General approach — The assessment of a patient with new bone pain may suggest the need for radiation therapy or an intervention such as kyphoplasty or surgery.

Patients with multifocal pain usually are managed with a nonsteroidal antiinflammatory drug (NSAID), unless they have a specific contraindication to use of these agents, and an opioid, with or without an adjuvant analgesic used specifically for bone pain.

Adjuvant analgesics to consider in this setting include ***osteoclast inhibitors (bisphosphonates, denosumab), glucocorticoids, and bone-seeking radionuclides.***

- We recommend the use of an **osteoclast inhibitor** in conjunction with an opioid in patients with symptomatic bone metastases from a variety of cancers. These drugs prevent skeletal-related events and improve quality of life, although their analgesic effects are only modest.

- **Glucocorticoids** may be useful in patients with opioid-refractory bone pain, especially in patients with advanced illness or a **"pain crisis,"** which is defined as severe and escalating pain that is not responding sufficiently to an opioid.

- Use of bone-targeted radiopharmaceuticals, such as **radium-223**, is typically reserved for the patient with multifocal bone pain that is refractory to other treatment. The majority of the data on efficacy are in patients with metastatic prostate cancer.

D. DRUGS FOR BOWEL OBSTRUCTION

Bowel obstruction is a well-recognized complication in patients with advanced intraabdominal or pelvic tumors. Most of these patients are inoperable, and their survival is generally short. Some cases may be amenable to placement of a self-expanding metal stent.

More recently, medical management of inoperable patients has focused on adequate control of pain, distention, and vomiting using hydration, opioids, and adjuvant medications that may reduce symptoms by lessening peritumoral edema **(glucocorticoids)** and diminishing intraluminal secretions and peristaltic movements **(anticholinergic agents and octreotide).**

"I need to pooh.na"

V. INTERVENTIONAL THERAPIES

The term "interventional" usually is applied to a group of invasive analgesic therapies, including injection-based treatments, catheter-based infusion therapies, implanted devices, and some surgical approaches.

Trigger point injection – Trigger point injections are used to address focal musculoskeletal pain, including pain that occurs in patients with cancer. Trigger points are distinguished from tender points or regions because they are associated with palpation-induced radiation of pain and taut bands in muscle. In practice, however, injections are often considered for any focal area in muscle or connective tissue that is associated with significant tenderness or pain on motion.

Joint injections – Patients with cancer commonly have painful comorbidities, such as osteoarthritis. Just as injection of a glucocorticoid into a painful joint is widely applied in populations without cancer, it may be considered to treat a painful joint in the cancer population.

Spine-related injections for back or neck pain — Low back or neck pain may represent important comorbidities in patients with cancer, either related or unrelated to the malignancy. Injections that are commonly performed to address acute and chronic, non-cancer, low back and neck pain may be appropriate in some cancer patients, including epidural steroid injections, facet joint injections, facet denervation approaches, and sacroiliac injections.

Vertebral augmentation procedures — Vertebroplasty and kyphoplasty are accepted options for carefully selected patients with symptomatic pathological vertebral fractures without epidural disease or retropulsion of bone fragments into the spinal cord and with pain that is refractory to noninvasive therapies. Vertebroplasty and kyphoplasty are percutaneous injection techniques that may reduce pain and, in some cases, stabilize the fracture. Vertebroplasty involves the percutaneous injection of bone cement (methylmethacrylate) under fluoroscopic guidance into a collapsed vertebral body. Kyphoplasty involves the introduction of inflatable bone tamps into the vertebral body; once inflated, the bone tamps variably restore the height of the vertebral body while creating a cavity that can then be filled with viscous bone cement.

Diagnostic nerve block — A diagnostic nerve block is performed in an effort to better understand the "generator" of the pain or the neural basis for afferent transmission of noxious stimuli. Local anesthetic (LA) blocks of somatic nerves, which interrupt both sensory and motor neural activity, can be useful in localizing the afferent pathway involved in sustaining the pain.

Prognostic nerve block — Prognostic blocks using LA are performed prior to planned neurolytic procedures to determine whether denervation is likely to relieve the pain and whether the sensory loss is tolerable.

Therapeutic block — Therapeutic nerve blocks are those that are intended to produce sustained pain relief or to address the underlying anatomic pathway involved in the patient's pain. These may be

broadly divided into those that block nerve transmission without permanently injuring the affected nerve (***nonneurolytic***) and those that permanently alter the nerve (***neurolytic***).

Sympathetic block of these structures may be performed using a bolus injection of LA. Following a successful LA injection, a neurolytic block may be performed for cancer patients with advanced disease and intractable pain in the hope of achieving long-term relief.

- **The stellate ganglion** is formed from fusion of the first thoracic and inferior cervical sympathetic ganglion, and it receives innervation from the T1-T4 sympathetic outflow. Stellate ganglion blockade provides sympathetic interruption of the head, neck, upper extremities, and intrathoracic structures. The block is performed by injection of LA near the ganglion where it lies on the anterior surface of the vertebral column, through placement of a needle in the anterior neck.
- **The lumbar sympathetic trunk** consists of sympathetic fibers that originate in the lower thoracic and L2 segments. Lumbar sympathetic block is performed to relieve pain in the lower extremities. Blockade is classically achieved through a paraspinous approach, with injection at the anterior lateral aspect of the vertebral body on the side of the painful extremity.
- **Celiac plexus, superior hypogastric plexus, and ganglion impar blocks** are performed to relieve visceral abdominal and pelvic pain. They are used to block sympathetic nerves that originate from T5 to L2 and distribute through the greater (T5-T10), lesser (T10-T12), and least (T12-L2) splanchnic nerves, coalescing in the celiac plexus, superior hypogastric plexus, and ganglion impar. These sympathetic nerves also carry visceral afferents, including nociceptors.

VI. ADVANCED NEURAXIAL TECHNIQUES

Neuraxial techniques include many of the spinal injections discussed above, most commonly including epidural steroid injections.

Advanced neuroaxial techniques (ie, neurostimulation and catheter-based neuraxial infusion) may be used to provide analgesia without the side effects of systemic pharmacotherapy. Proper patient selection is important for the appropriate use of these interventions. The main disadvantages of these techniques are cost, risk of infection, and mechanical failure.

A. Spinal cord stimulation — The most common type of implanted neurostimulatory treatment is spinal cord stimulation (SCS; dorsal column stimulation). SCS involves percutaneous or surgical implantation of electrodes in the epidural space, with power supplied by an implanted battery.

B. Neuraxial infusion — Continuous infusion of medications into a neuraxial space (ie, epidural or intrathecal is also called targeted drug delivery. Several drugs and infusion devices are available for neuraxial infusion.

I. PSYCHOLOGICAL APPROACHES

Over the past 20 years, psychological approaches have increasingly become part of a comprehensive approach to pain management. This has been prompted by the recognition of the ongoing interplay of physical and psychological variables in the perception and management of pain. As pain is a multidimensional experience, not only is it affected by cognitive and psychological variables but, in turn, it does affect patients' cognition and their psychological response. Even when there are clear physiological mechanisms underpinning and sustaining pain, as in the case of patients with cancer, minimizing its impact on mood and overall emotional well-being can improve patients' quality of life. This section on psychological approaches will focus on cognitive behavioral therapy, because it is the modality that has received support in randomized trials.

Cognitive-behavioral therapy —Cognitive-behavioral therapy (CBT) approaches to management of cancer pain can effectively ***improve coping, self-efficacy, and a sense of control over the pain***.

According to the cognitive-behavioral model, an individual's interpretation of external events and bodily sensations directly affects his or her emotional reactions to these events and subsequent behavior. Every cognitive behavioral approach starts by identifying and modifying unhelpful thinking patterns that are believed to increase distress. Dichotomous thinking, catastrophization, and overgeneralization, among others, are considered dysfunctional cognitive patterns because they typically arise from limited information and do not accurately reflect reality.

The goal of CBT is to present the patient with a reality-based alternative version or interpretation of events, in order *to elicit a more adaptive emotional response and improved coping*. As an example, a patient with early stage cancer who is experiencing pain may interpret the situation as hopeless, focusing on interpreting the pain as a sign that the illness is progressing, that death is a likely outcome, and there is nothing that can be done. The result of this thought process may be significant emotional distress, and an increase in anxiety, depression, and overall suffering. A cognitive-behavioral intervention would encourage the patient to explore additional meanings of the pain that might allow for a greater sense of control.

II. REHABILITATION AND PHYSICAL MEDICINE INTERVENTIONS

The primary goal of rehabilitative interventions may be functional improvement, symptom control, or both. Interventions include therapeutic exercise, usually initiated or guided by a physical therapist; hydrotherapy, which may be particularly helpful in the medically ill; orthoses, ambulation aids, and other devices; and "physical modalities" such as the application of heat and cold, vibration, ultrasound, electrical stimuli (eg, as with a transcutaneous electrical nerve stimulation [TENS] device), and therapy for lymphedema. Therapeutic massage is discussed in a separate section.

A. Therapeutic exercise — Therapeutic exercise (physical therapy) involves the systematic implementation of planned physical movements, postures, or activities designed to ameliorate

impairment, improve function, and enhance overall wellbeing. Manual stretching, myofascial therapy, passive mobilization, and active exercises are some of the modalities utilized within this approach.

Patients with a musculoskeletal basis to their pain may be able to achieve better symptom control and potentially better function through focused physical therapy that specifically targets the painful region. Improved pain and wellbeing may also result indirectly, presumably due to the physiologic benefits associated with conditioning and/or exercise-induced increases in the endogenous endorphins and enkephalins. Some other benefits of therapeutic exercise include favorable effects on blood pressure, promotion of muscle strength and flexibility, and improvement in aerobic capacity and hormonal adaptation. A systematic review of 18 randomized studies that investigated various applications of physical therapy on impaired range of motion and pain of the upper limb after breast cancer treatment demonstrated the effectiveness of physical therapy for improving postoperative pain and range of motion.

Therapists and physiatrists must work with oncologists to confirm the safety and appropriateness of exercise, and clarify the medical status of the patient and the specific targets and goals of care. Therapeutic exercise can be a time-limited intervention that may ameliorate symptoms and improve function after disease-modifying therapy, such as surgery or chemotherapy, or, in patients with advanced illness, to reduce symptom distress and improve self-efficacy and quality of life. The type, frequency, and duration of exercise is always informed by the performance status of the patient and the overall goals of care.

B. Hydrotherapy — Hydrotherapy is an approach used in disorders, such as rheumatoid arthritis, ankylosing spondylitis, and fibromyalgia, which are characterized by severe pain and impairment. Although never systematically studied in patients with cancer-related pain, hydrotherapy may be of benefit for selected cancer patients after consultation between the physiatrist and the oncologist. Hydrotherapy involves the submersion of a small or large body surface area, usually in a small tank or tub. The water temperature usually does not exceed 40° C, but it can be adjusted depending on the condition being treated and the desired effect.

Hydrotherapy provides a ***reduced-gravity environment*** that facilitates benefit from physical therapy because of the effect of buoyancy and decreased stress on joints. Additionally, hydrotherapy facilitates muscle relaxation and improves overall emotional state. Patients may experience a decrease in the typical pain experienced with movement, and this may enhance both physical and psychological outcomes.

C. Orthoses and other devices — Examples of orthoses include:

- Immobilizers of the shoulder and arm for a painful brachial plexopathy
- Corsets for persistent pain after treatment for vertebral metastases
- Wrist or ankle splints for distal extremity weakness or pain related to neuropathy.

Patients with pain on movement may benefit from a splint that is designed to limit those motions that incite the pain. In the cancer population, and particularly in the setting of advanced illness,

the use of an orthosis may be preferable to other interventions, such as physical therapy, that attempt to improve function. A return to full function may not be possible, or it may not be the primary treatment goal. Evaluation by an occupational therapist, with input by the oncologist, can clarify the availability and cost of various options.

Stump pain may be ameliorated by a well-fitting prosthesis, an ambulation aid may reduce pain exacerbation with walking, and devices designed to facilitate specific functions such as toileting or eating can have analgesic consequences or reduce the risk of secondary painful complications related to immobility.

D. Physical modalities — The therapeutic application of heat or cold, ultrasound, and electrical nerve stimulation to focal sites of pain that are unrelated to cancer (eg, sprains) is widely accepted. However, there have been very few studies evaluating short-term efficacy, long-term effectiveness, and safety of these physical modalities in populations with cancer pain, and the evidence in other populations is extremely limited.

Physical modalities may be especially **useful as adjuncts** for mild to moderate pain and while awaiting the effect of a breakthrough analgesic. They are never adequate alone for managing moderate or severe cancer pain. There are no comparative data to guide suggestions concerning the selection of specific modalities when used as adjunctive treatment for pain, and the choice of technique is empirical. Based on inference and concern about adverse cutaneous effects, guidelines often suggest avoiding the topical application of these stimuli to areas with reduced sensation and those that are directly superficial to tumor masses.

Cold — Cold application with ice packs, malleable chemical gel packs, and vapocoolant sprays may reduce muscle spasm, inflammation, and edema. The mechanism of action is an initial vasoconstriction, followed by vasodilation. Despite widespread use, there are no controlled studies of cold-induced analgesia for cancer pain. Application of cold should be avoided in ischemic and irradiated tissues.

Heat — Various superficial and deep heating methods have been applied to control pain and are popular among cancer pain patients. Heat is analgesic in part by increasing blood flow and decreasing joint stiffness. It also may induce a state of mental relaxation. Superficial heating with hot packs, medicated heat patches (eg, containing capsaicin [0.025%]), heating pads, or baths improves cutaneous blood flow and relaxes muscles and ligaments to a depth of 0.5 cm.

TENS and other electrostimulation devices — Transcutaneous electrical nerve stimulation (TENS) is widely used, despite insufficient evidence to confirm efficacy in any type of chronic pain, including cancer-related pain. Case reports and uncontrolled studies suggest efficacy, although the duration of benefit may be limited.

Scrambler therapy — Scrambler therapy is a novel and noninvasive approach developed for the management of pain. It is delivered through an electrocutaneous nerve stimulation device (Calmare) by applying EKG-like pads bilaterally on the skin, above and below the site of pain. Unlike the TENS unit,

scrambler therapy does not deliver the stimulation directly to the painful area. The nerve stimulation device is designed to “scramble” afferent pain signals and replace them with non-painful stimuli.

Lymphedema treatment — Lymphedema related to cancer treatment is common and often painful. Rigorous physical therapy protocols for lymphedema include specific education focused on skin care and avoidance of trauma, manual lymph drainage, intermittent pneumatic compression, compression bandaging, and exercises. If the girth in the affected limb can be reduced, patients usually experience a decline in uncomfortable heaviness or stretch, and in secondary myofascial pains.

III. INTEGRATIVE THERAPIES

Integrative therapy may be viewed as a care model in which conventional medical approaches are combined with any of a large number of so-called complementary treatments. This strategy is explicitly intended to pursue a holistic course that includes specific objectives (eg, pain control and management of other distressing symptoms) with a broader goal to improve overall quality of life. These approaches are becoming increasingly popular among patients with cancer worldwide. Use of integrative therapies is especially prevalent among women with breast cancer.

The National Institutes of Health suggests the following broad categories of integrative treatments:

- Alternative medical systems, such as Traditional Chinese Medicine (TCM), Ayurveda, homeopathy, and naturopathy
- Mind-body interventions, such as meditation, hypnosis, dance, music and art therapy, prayer, and mental healing
- Biological-based therapies, such as herbal therapies, specialized diet therapies, orthomolecular nutrition, and individual biological therapies
- Manipulative and body-based methods, such as massage and chiropractic
- Energy therapies, such as biofield and bioelectromagnetic-based therapies

Tips from DOC NIC

R – Read

U – Understand

R – Remember

A – Apply

L – Like (and share)