



ISSN: 0975-766X
CODEN: IJPTFI
Review Article

**Available Online through
www.iiponline.com**

CANCER PAIN ASSESSMENT AND MANAGEMENT: AN OVERVIEW
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Received on 13-08-2011

Accepted on 26-08-2011

Abstract

Pain is one of the most common problems in cancer patients. About 80% of patients living with advanced cancer experience pain. The cancer pain occurs due to cancer itself probably by the pressure on one of the body's organs, bone, nerves, and blood vessels. It may be due to cancer treatment such as use of chemotherapy which produces numerous side effects and ultimately pain. Radiotherapy and the surgical treatment make contribution to produce pain. There are different types of cancer pain such as somatic pain, visceral pain, neuropathic pain, bone pain and the radiation, chemotherapy related neurotoxicity. Comprehensive pain assessment is one of the most important initial steps for successful management of cancer pain. To help introduce objectivity in the evaluation, a number of pain scales have been utilized to quantify pain intensity. Proper assessment of the cancer is important for pain management. Different parameters are required to be considered while assessing cancer pain this includes intensity, location, quality, timing, meaning of pain, aggravating factors. Adequate pain management is possible only with thorough patient assessment and frequent reassessment. Since uncontrolled pain can have an adverse impact on patients and their families, optimal management of pain should be a priority goal for all clinicians. Pain may be due to tumor infiltration of local structures or to antineoplastic therapy, or it may be unrelated to the tumor. Two approaches are available to manage the cancer pain which includes pharmacological approach and non-pharmacological approach. Proper treatment rotation is followed to avoid tolerance, dependence and side effect of drugs. Successful long-term management requires continuity of care that provides an appropriate level of monitoring

and responds quickly, flexibly, and expertly to the changing needs of the patient. The proper assessment and reassessment of cancer pain is important for management of cancer pain and attainment of optimal quality of life. As the knowledge in field of neuropharmacology, various chemical mediators and signaling pathway responsible for pain sensation suggest that many new approaches are coming to control pain. As the survival of patients with cancer becomes longer, reliable pain relief is now a high-priority issue that warrants both scientific research and industrial development of new devices and pharmaceutical agents that would make this pain relief complete, safe, and lasting. So, it is important to investigate new drugs and new techniques for controlling cancer pain.

Key Words: Cancer pain, management, assessment

Introduction

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both”.^[1] This definition recognizes that pain is a perception and not a sensation. One influential model described pain in terms of three hierarchical levels: a sensory-discriminative component (*e.g.*, location, intensity, quality), a motivational–affective component (*e.g.*, depression, anxiety), and a cognitive-evaluative component (*e.g.*, thoughts concerning the cause and significance of the pain). Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (*e.g.*, stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (*e.g.*, terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling. These properties illustrate the duality of pain it is both sensation and emotion. When acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (*e.g.*, limb flexion, abdominal wall rigidity) is often present.^[2] An acceptable definition of pain remains an enigma. Once thought to be a punishment from the gods, the word is derived from the Latin *peone* and the Greek *poine*, meaning “penalty” or “punishment.” Aristotle considered pain a feeling and classified it as a passion of the soul, where the heart was the source or processing

center of pain. This Aristotelian concept predominated for 2,000 years, although Descartes, Galen, and Vesalius postulated that pain was a sensation in which the brain played an important role. ^[3] In the 19th century, Mueller, Van Frey, and Goldscheider hypothesized the concepts of neuroreceptors, nociceptors, and sensory input. These theories developed into the current definition of pain: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Pain often is so subjective, however, that many clinicians define pain as whatever the patient says it is. The best care is achieved when the patient comes first. There is an important implication of both the IASP definition and the hierarchical model of pain: As a perception, pain may or may not correlate with an identifiable source of injury. The activity in the body’s “nociceptive” system, which senses noxious stimuli and generates a physiological and behavioral response, can be initiated by injury and sustained by neuroplastic changes even after healing; activity in this system can occur in the absence of any discrete injury but in association with a recognizable disease. In some cases, pain can develop and be unrelated to any identifiable physical process. In all cases, the reality that pain is a perception indicates the potential for profound influence of psychological and emotional factors, cognitions, and varied external events. ^[1] There is another important implication of the concept of pain as perception: It is almost always best to believe that the patient is experiencing what is being reported. Because there is no objective indicator for pain, experts agree that the best clinical approach in most circumstances is to assume that the patient is reporting a true experience, even in the absence of a clear explanation. Importantly, accepting a patient’s complaint of pain as valid does not require clinical identification of a physical cause, or demand the initiation of a specific treatment. Pain occurs whenever any tissues are being damaged, and it causes the individual to react to remove the pain stimulus. Even such simple activities as sitting for a long time on the Ischia can cause tissue destruction because of lack of blood flow to the skin where it is compressed by the weight of the body. When the skin becomes painful as a result of the ischemia, the person normally shifts weight subconsciously. But a person who has lost the pain sense, as after spinal cord injury, fails to feel the pain and, therefore, fails to shift. This soon results in total breakdown and desquamation of the skin at the areas of pressure. ^[4]

Epidemiology

Fifty million Americans are partially or totally disabled because of pain. The annual cost of pain to U.S. society can be estimated to be in the billions of dollars. In 1 year, an estimated 25 million Americans will experience acute pain due to injury or surgery, and one third of Americans will experience severe chronic pain at some point in their lives. These numbers are expected to rise, as increasingly more Americans work beyond age 60 years and survive into their 80s. Unfortunately, pain often remains undertreated in hospitals, long-term care facilities, and the community. Seriously ill hospitalized patients have reported a 50% incidence of pain; 15% had extremely or moderately severe pain occurring at least 50% of the time, and 15% were dissatisfied with overall pain control. ^[5] In a follow-up report, the author's state that pain control persists as a major problem in hospitalized patients, and some of these patients were still in pain many months after hospitalization and experienced pain even on their deathbeds. In addition, problems with inadequate use of analgesics have been reported in cancer patients residing in nursing homes. In the Michigan pain study, 70% of chronic pain patients claimed to have pain despite treatment, with 22% believing that treatment worsened pain. Persistent pain is an escalating public health problem, currently affecting approximately 29% of Canadians. It is anticipated to affect one in three Canadians over the next two decades. ^[6] Pain is the most common reason why Canadians seek help from health professionals; 21.5% of patients seen by primary care physicians suffer from persistent pain. According to a nationwide survey conducted in the United States, 44% of adults report that they have acute pain and 19% suffer from chronic pain. ^[7]

Types of pain

- **Acute pains**

Acute pain can be a useful physiologic process warning individuals of disease states and potentially harmful situations. Acute pain usually is nociceptive, although it can be neuropathic in nature, with a relatively strong relationship to levels of pathology. Common causes of acute pain include surgery, acute illness, trauma, labor, and medical procedures. Acute pain signals injury to the body resulting from trauma, surgery, or disease process that damages tissue. Acute pain is short lived (typically less than one month) and goes away when the condition causing

it improves or goes away. People often describe acute pain as sharp, stabbing, or burning. Physical signs that accompany acute pain include: rapid breathing, rapid heart rate (tachycardia), elevated blood pressure, clammy skin, dilated pupils. Severe acute pain may cause loss of consciousness; severe pain requires prompt or emergency medical evaluation. ^[9]

- **Chronic pain**

Under normal conditions, acute pain subsides quickly as the healing process decreases the pain-producing stimuli; however, in some instances, pain persists for months to years, leading to a chronic pain state with features quite different from those of acute pain. This type of pain can be nociceptive, neuropathic/ functional, or both. Subtypes include: pain that persists beyond the normal healing time for an acute injury (e.g., complex regional pain syndrome), pain related to a chronic disease (e.g., pain secondary to osteoarthritis), pain without an identifiable organic cause (e.g., fibromyalgia), and a fourth type that many experts believe warrants a discrete classification, pain associated with cancer. Chronic pain is very common, affecting the daily lives and activities. The most prevalent causes of chronic pain are low back pain, arthritis, and headache. ^[9]

- **Cancer Pain**

Pain associated with potentially life-threatening conditions is often called malignant pain or simply cancer pain. This type of pain includes both chronic and acute components and often has multiple etiologies. It is pain caused by the disease itself (e.g., tumor invasion, organ obstruction), treatment (e.g., chemotherapy, radiation, surgical incisions), or diagnostic procedures (e.g., biopsy).

- **Eudynia**

Pain that exists as a symptom clearly associated with an underlying health condition or circumstance and results from stimulation of nociceptors (specialized sensors on the dendrites of neurons that convey pain messages). Eudynia also called acute pain, is typically short lived. Such pain is a common feature of injury and numerous diseases processes and is the body's signal that something is wrong. ^[3]

- **Headache**

Pain perceived as coming from the face and head. There are numerous types of headache resulting from various causes. Among them are tension headache, migraine headache, cluster headaches, sinus headache, and rebound headache. Headache may also indicate hypertension (high blood pressure), transient ischemic attack or stroke. Headache also is common with colds, flu, and fever. Very rarely headache may signal an infection such as meningitis or an aneurysm or a tumor in the brain. The nerves in the soft tissue of the head, neck, and face transmit the pain signals familiar as headache. There are no sensory nerves in the brain or bones of the skull, even though headache pain often feels as though it comes from deep within the head. Pain associated with events within the brain, such as tumor or stroke, arise from the increase in pressure within the cranium (enclosure of the skull) these conditions cause. The pressure stimulates the network of nerves that interlace with blood vessels at the base of the brain. This nerve and blood vessel network extends into the soft tissue surrounding the skull, magnifying the perception of pain.^[10]

- **Maldynia**

The defining characteristic of maldynia is that the pain does not activate specific pain receptors (nociceptors) or follow conventional pain pathways. Some researchers believe maldynia represents a malfunction of the brain's pain interpretation processes, likely an imbalance among brain neurotransmitters. Other researchers believe maldynia represents disturbances in the body's pain sensory mechanisms, perhaps changes at the level of the neuron that alter the sensitivity of pain signals. Maldynia is an extraordinarily frustrating condition.^[10]

- **Neurogenic pain**

Pain that results from dysfunction of the nociceptors, specialized molecules on the dendrites of neurons that detect pain and initiate transmission of pain signals to the central nervous system. Neurogenic pain often follows an injury (traumatic or surgical) for which pain is a reasonable symptom. However, when the injury heals, the nociceptors can remain hypersensitive to stimuli, particularly touch and temperature, which they perceive as painful, and the nociceptors continue to initiate pain signals. Neurogenic pain often accompanies degenerative neurologic conditions

such as multiple sclerosis and pain syndromes such as trigeminal neuralgia and complex regional pain syndrome.

The sensation of neurogenic pain is characteristically that of a persistent tingling, burning, or “pins and needles” feeling. Some people also feel sharp stabs of pain. ^[5]

- **Phantom pain**

The sensation of pain that feels as though it came from an amputated limb or other body part. Researchers believe phantom pain results from continued activity, after the amputation, among neurons in the brain that interpret nerve signals. Severed nerve fibers near the site of the amputation continue to send signals even though the surgery has removed most of their nociceptors (molecules that detect stimuli as pain). The remaining portions of the nerves continue to function, and the brain interprets their incomplete messages as pain signals. The pain often feels of the same nature as pain that might have been present in the limb before the amputation. Many people who have phantom pain also have stump pain (pain in the remaining portion of the limb). Stump pain generally results from the damage to the nerves at the site of the amputation. ^[9]

- **Psychogenic pain**

A pain disorder in which the pain the person experiences has no apparent organic or physical basis. Psychogenic pain often has accompanying psychological components such as anxiety or depression. Recurring headache, back pain, generalized muscle pain, and stomach pain are common presentations of psychogenic pain. In psychogenic pain, the experience of pain is as real as if there were a clear physical cause. However, over time the nature of the pain deviates from the characteristics the doctor would expect to observe with pain of organic cause. The intensity of the pain may vary with external circumstances, for example, rather than as a result of physiologic changes that would reasonably bring about increase or decrease in pain intensity. Psychogenic pain may be acute (come on suddenly) or chronic (persist over an extended time). ^[10]

- **Terminal pain**

Pain that results from the end stages of disease processes such as cancer, cardiovascular disease and aids. Doctors consider a health condition to be terminal when the person is likely to live less than six months. Terminal pain

occurs because damage to the tissues and structures of the body is extensive and widespread. The damage often directly involves nerves. ^[11]

- **Referred pain**

A person experiences referred pain at a location some distance from the source of the pain. The location is sometimes so far removed from the source of the pain that the person does not connect the pain with its cause. For example, gall stones in the gallbladder often cause pain in the upper back beneath the shoulder blade. Pain associated with heart attack may occur as referred pain to the left arm, shoulder, neck, and lower jaw. ^[11]

Current scenario

Worldwide 70-80% of peoples are suffering from pain that may be due to disease, treatment, psychological factors. Because of improper assessment of pain the patient may not receive appropriate medicine treatment to treat the pain. There is a gap between patient explanation and physician understanding about the pain syndrome. Hence there is a need to improve knowledge about the pain. it is also necessary to investigate such pharmacological and non-pharmacological treatment to control the pain and which having lesser side effect and which improves patients life.

Pathophysiology of pain

The pathophysiology of pain involves a complex array of neural networks in the brain that are acted on by afferent stimuli to produce the experience we know as pain. In acute pain, this modulation is short-lived, but in some situations, the changes may persist, and chronic pain develops.

- **Stimulation**

The first step leading to the sensation of pain is stimulation of free nerve endings known as nociceptors. These receptors are found in both somatic and visceral structures. They distinguish between noxious and innocuous stimuli, and they are activated and sensitized by mechanical, thermal, and chemical impulses. The underlying mechanism of these noxious stimuli (which in and of themselves may sensitize/stimulate the receptor) may be the release of bradykinins, potassium ion (K⁺), prostaglandins, histamine, leukotrienes, serotonin, and substance P (among others)

that sensitize and/or activate the nociceptors. Receptor activation leads to action potentials that are transmitted along afferent nerve fibers to the spinal cord. ^[13]

- **Transmission**

Nociceptive transmission takes place in A δ and C-afferent nerve fibers. Stimulation of large-diameter, sparsely myelinated A fibers evokes sharp, well-localized pain, whereas stimulation of unmyelinated, small-diameter C fibers produces dull, aching, poorly localized pain. These afferent, nociceptive pain fibers synapse in various layers (laminae) of the spinal cords dorsal horn, releasing a variety of neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide. The complex array of events that influence pain can be explained in part by the interactions between neuroreceptors and neurotransmitters that take place in this synapse. For example, by stimulating large sensory myelinated fibers (e.g., A β) that mutually connect in the dorsal horn with pain fibers, both noxious and nonnoxious stimuli can have an inhibitory effect on pain transmission. Functionally, the importance of the interplay between these different fibers and various neurotransmitters and neuroreceptors is evident in the analgesic response produced by topical irritants or transcutaneous electrical nerve stimulation. These pain-initiated processes reach the brain through a complex array of at least five ascending spinal cord pathways, which include the spinothalamic tract. Information other than pain is also carried along these pathways. Thus, pain is influenced by many factors supplemental to nociception and precludes simple schematic representation. It is postulated that the thalamus acts as a relay station, as these pathways ascend and pass the impulses to central structures where pain can be processed further. ^{[14][15]}

- **Pain Perception**

At this point in transmission, pain is thought to become a conscious experience that takes place in higher cortical structures. The brain may accommodate only a limited number of pain signals, and cognitive and behavioral functions can modify pain. Relaxation, distraction, meditation, and guided mental imagery may decrease pain by limiting the number of processed pain signals. In contrast, a change in our neurobiochemical makeup that results in states such as depression or anxiety may worsen pain. ^{[11][13]}

- **Modulation**

The body modulates pain through a number of complex processes. One, known as the endogenous opiate system, consists of neurotransmitters (e.g., enkephalins, dynorphins, and β -endorphins) and receptors (e.g., μ , δ , and κ) that are found throughout the central nervous system (CNS). Like exogenous opioids, endogenous opioids bind to opioid receptor sites and modulate the transmission of pain impulses. Other receptor types also can influence this system. Activation of N-methyl- D-aspartate (NMDA) receptors, found in the dorsal horn, can decrease the μ -receptors' responsiveness to opiates. The CNS also contains a highly organized descending system for control of pain transmission. This system can inhibit synaptic pain transmission at the dorsal horn and originates in the brain. Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine, γ -aminobutyric acid (GABA), and neurotensin. ^{[11][12]}

Neurophysiology of cancer pain

It is estimated that 70% to 90% of patients with advanced cancer experience significant pain. Since uncontrolled pain can have an adverse impact on patients and their families, optimal management of pain should be a priority goal for all clinicians. Cancer pain syndromes can be classified as somatic, visceral, or neuropathic in origin. Pain may be due to tumor infiltration of local structures or to antineoplastic therapy, or it may be unrelated to the tumor. Recognition of pain syndromes is essential for the adequate management of cancer pain. Basic science research on the mechanisms of pain has been helpful in providing the scientific rationale for new approaches to cancer pain management. This article reviews the neurophysiology of pain, with an emphasis on the understanding and treatment of cancer pain syndromes. The goals of palliative care are to control symptoms in patients with advanced disease and enhance their quality of life. Despite the growth of palliative care in this country, the majority of patients die outside of their homes, and many do not receive adequate control of their symptoms.^[16] The Robert Wood Johnson Foundation found that although 81% of patients stated that they had a clear preference for dying at home, 56% died in a hospital. Although education and training have increased for physicians and nurses in the management of pain,

many patients do not receive adequate analgesia. More than 70% of cancer patients report pain and more than 36% of patients with metastatic disease have pain severe enough to impair function. Pain also can be psychologically devastating because it can be a constant reminder of the incurable and progressive nature of the disease. [21][22]

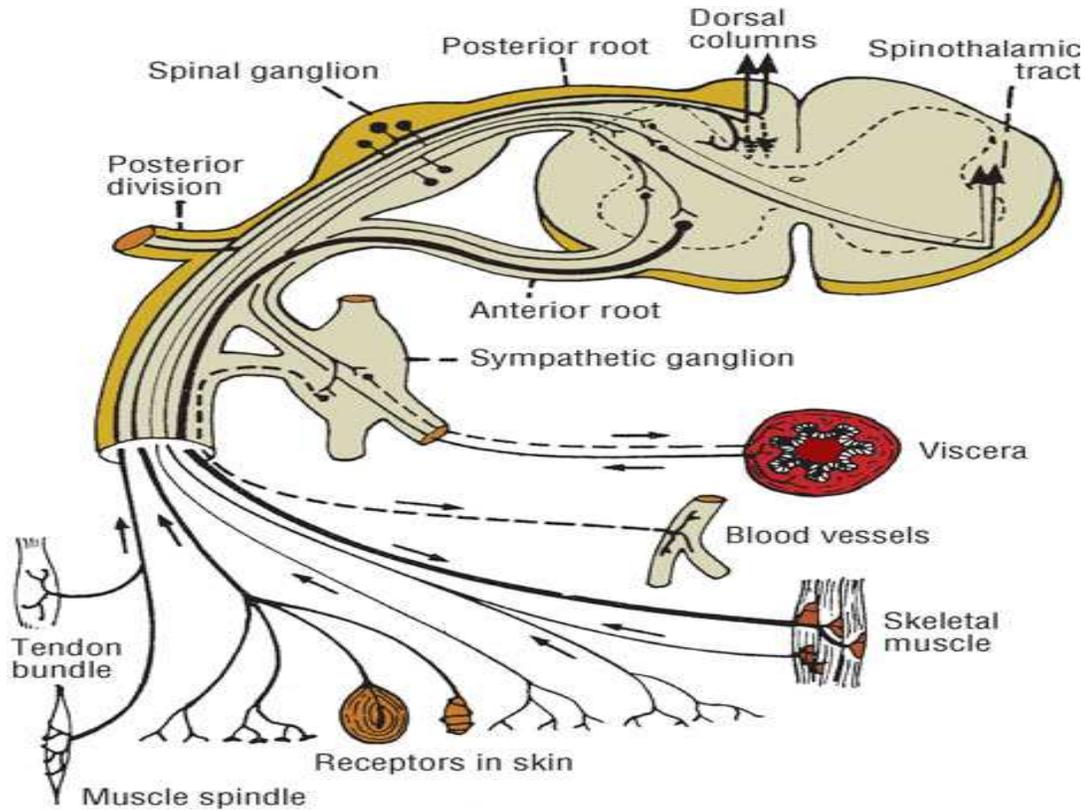


Figure: 1- Pain pathway

Causes of cancer pain

- **Tumour-related nociceptive pain syndromes:**

Neoplastic invasion of bone, joint, muscle, or connective tissue can cause a persistent somatic pain; bone pain syndromes are the most common. Only a small proportion of bone metastases become painful, and the factors that convert a painless lesion into a painful one are unknown. The spine is the most common site of bone metastases and many patients with cancer have back pain. Extension of a neoplasm from the vertebra has the potential to damage the spinal cord or nerve roots, and thereby produce substantial neurological compromise. Back pain from vertebral metastasis is, therefore, a marker of potential epidural spinal cord or nerve root compression. Obstruction, infiltration, or

compression of visceral structures, including hollow viscous and supporting connective tissues, produce various visceral nociceptive pain syndromes. [23]

- **Tumour-related neuropathic pain syndromes:**

Neuropathic pain syndromes may be caused by tumour infiltration or compression of nerve, plexus, or roots, or by the remote effects of malignant disease on peripheral nerves. The syndromes are highly variable; patients may have aching pains or dysesthesias (abnormal pain sensations such as burning) anywhere in the dermatomal region innervated by the damaged neural structure. [23]

- **Treatment-related pain syndromes:**

Nociceptive pain syndromes related to chemotherapy, radiation therapy, or surgery is rare. Somatic pain related to osteonecrosis of bone can be caused by radiation or corticosteroid-based chemotherapy regimens, and chronic visceral pain can follow intraperitoneal chemotherapy or abdominal radiation therapy. These syndromes can mimic tumour-related pains and in the assessment it is important to exclude recurrence. Most post-treatment pain syndromes are neuropathic. The factors that predispose some patients to chronic neuropathic pain after nerve injury, the extent or severity of which may be minor, are unknown. Any surgical incision could lead to a neuropathic pain syndrome in a small proportion of patients. Repeated assessments are often needed to exclude tumour recurrence. Chronic pain after any amputation can result in neuroma formation at the amputation site, the underlying cause of stump pain, or central-nervous-system processes that presumably underlie the development of phantom pain. Radiation-induced fibrosis can damage a peripheral nerve or nerves and cause chronic neuropathic pain. [23]

Types of cancer pain

- **Somatic Cancer Pain**

Somatic cancer pain can be caused by neoplastic invasion of bone, joint, muscle, or connective tissue. The local tumour mass produces and stimulates local production of inflammatory mediators, causing ongoing stimulation of peripheral nociceptors. Other sources of somatic cancer pain include bone fractures, reactive spasm of muscle overlying an area of tissue damage, postsurgical incisional pain, and radio/ chemotherapy-induced pain syndromes.

The most prevalent somatic pain syndromes are related to neoplastic bone involvement. Bone pain may be acute, chronic, or incidental in nature. It is typically dull, varies in intensity, causes local tenderness, and is exacerbated by weight-bearing or movement.^{[16][24]}

- **Bone Pain**

Direct tumour invasion of bone or the development of osseous metastases may account for persistent bone pain. Not all bone metastases are painful, and the pain is often disproportionate to the radiological findings. Nociceptive afferents are most concentrated in the periosteum, whereas bone marrow and cortex are less sensitive to pain. Some of the mechanisms contributing to neoplastic bone pain include stretching of the periosteum by tumour expansion, local microfractures that cause bony distortion, nerve compression due to either collapsed vertebrae or direct tumour encroachment, and local release of algescic substances from the bone marrow. Bone pain has been correlated with osteoclastic activity. In normal bone, the net activity of bone resorbing cells (osteoclasts) equals the net activity of bone-forming cells (osteoblasts). In metastatic disease, there is evidence of increased osteoclastic activity. Both tumor and humoral factors, including prostaglandins, cytokines, local growth factors, and parathyroid hormone, enhance osteoclastic activity and act locally to stimulate nociceptors. Despite increased osteoclastic activity, bone formation also increases. With this increased turnover of bone, the proportion of immature, undermineralized bone increases and thus the likelihood of fracture increases. The metabolic activity of bone is a predominantly surface-based phenomenon. Since cancellous bone provides a large surface area compared with cortical bone, it is not surprising that neoplastic disorders of bone remodeling are expressed earlier at cancellous sites. It is likely that a combination of peripheral and central mechanisms contributes to pain associated with bony metastases.^{[16][24]}

Peripheral mechanism: Periosteum is well innervated and the sensory free nerve endings present are thought to be involved in the mediation of pain. Although the precise mechanisms are unclear, it is thought that excessive osteoclast-induced bone destruction leads to pain through stimulation of mechanoreceptors in the periosteum. Sensory nerve fibers may also be destroyed due to excessive osteoclastic activity and this may lead to neuropathic-

type pain. Sensory neurons in the periosteum are also affected by increased mechanical stress within the bone which may lead to pain and increased sensitization. This effect is enhanced by the presence of inflammatory cells within the tumor caused by an osteoblastic response, contributing to a local acidosis and in turn sensitizing acid sensing ion channels such as the transient receptor potential vanilloid receptor 1 (TRPV1). Studies have shown that TRPV1 is important in the integrative signaling in CIBP and inhibiting its release is important in controlling complex pain states. Tumor cells and tumor stromal cells secrete various inflammatory cells that contribute to the sensitization of excitation of primary afferent neurons, causing peripheral sensitization. One product that is significant in CIBP is nerve growth factor (NGF), which also acts to intensify nociceptive transmission in the dorsal horn.^{[16][17][19][20]}

Central Mechanism: It has been suggested that CIBP is a unique pain state showing physiological characteristics of both inflammatory and neuropathic pain and changes in dorsal horn cell phenotype. Whereas inflammatory pain states are characterized by up-regulation of calcitonin gene-related peptide (CGRP), and neuropathic pain states by up-regulation of neuropeptide Y (NPY), CIBP is distinct in that there is an up-regulation of dynorphin in the deep dorsal horn and increased expression of c-fos. In addition, it has been shown in rat models of CIBP that repetitive noxious stimulation of primary C-fiber afferents results in a “wind-up” phenomenon which is characterized by an escalation of nociceptive transmission by cells in the dorsal horn. Wind-up contributes to central sensitization via wide-dynamic range (WDR) cells resulting in the amplification and prolongation of nociceptive transmission in ascending pathways in the central nervous system. This sensitizing effect results in sensitivity to normally non noxious mechanical and thermal stimuli (allodynia) and exaggerated responses to noxious stimuli (hyperalgesia). Central sensitization is mediated via activation of the N-Methyl- d-aspartate (NMDA) glutamate receptor and is a feature of many chronic pain states.^{[16][17][19][20]}

- **Visceral Cancer Pain**

Certain clinical characteristics are peculiar to visceral pain. Some viscera are apparently insensitive to pain. Solid organs such as lung, liver, and kidney parenchyma are insensitive, despite gross destruction by malignancy, and pain is signaled only when capsular or adjacent structure is involved. Harmful stimuli such as burning or cutting of

visceral tissue do not cause pain, whereas a natural stimulus such as hollow-organ distension readily produces pain.

Visceral pain is often diffuse and poorly localized, and it is sometimes referred to other non visceral structures, making the source of the pain difficult to elucidate. Visceral pain may be accompanied by autonomic reflexes such as nausea. The physiological significance of these properties is not yet fully understood. Visceral pain arises from direct stimulation of afferent nerves due to tumor infiltration of the soft tissue or viscera. Stretching, distension, or ischemia of the viscera may cause visceral pain. This pain tends to be poorly localized and often ill defined. As already noted, visceral pain can be deep, aching, or colicky pain. In cancer patients, visceral pain may be caused not only by direct tumor infiltration, but also by variable conditions such as constipation, radiation, or chemotherapy.

[16][18][24]

Mechanisms of Visceral Pain

Receptors: Recent research has shown that there are two distinct classes of nociceptive sensory receptors in viscera. The first class is composed of “high-threshold” receptors that respond to mechanical stimuli within the noxious range. These have been identified within many viscera, including the heart, lungs, gastrointestinal tract, ureters, and urinary bladder. The second class is composed of receptors that have a low threshold to natural stimuli and encode the stimulus intensity in the magnitude of their discharges, the so-called “intensity-encoding” receptors. Both receptor types are mainly concerned with mechanical stimuli such as stretch and are involved in the peripheral encoding of noxious stimuli in viscera. Experimental data suggest that viscera contain nociceptive afferents that are normally considered “silent.” In the presence of local inflammation or tissue injury, these afferents become sensitized and respond to previously innocuous natural stimuli. The clinical significance of this inflammation-induced sensitivity is unknown. High-threshold afferents signal acute visceral pain. Local ischemia, hypoxia, and inflammation cause pain by sensitizing high-threshold receptors and these previously “silent” or unresponsive receptors. Inflammatory mediators released locally lower their firing threshold and, by peripheral sensitization, augment and perpetuate the transmission of noxious stimuli. [16][17]

Triggering Factors — Pain in visceral structures is not necessarily linked to tissue injury, but rather is dependent on the nature of the provoking stimulus. An adequate stimulus refers to the stimulus that produces a given sensation. Adequate stimuli that induce pain are distension, ischemia, and inflammation. Hollow organs such as the colon are very sensitive to luminal distension or inflammation but are totally insensitive to cutting or burning stimuli. Pain induced by colonic distension is dependent on the distending pressure rather than the volume. It has been shown that the intraluminal pressure in the colon required to produce a painful sensation is 40 to 50 mm Hg. Hence, a tumor may continue to grow undetected if it fails to exert this intraluminal pressure and may cause pain only at a much later stage when there is complete obstruction of the lumen and a significant rise in intracolonic pressure. Solid organs are least sensitive, whereas the serosal membranes of hollow organs are most sensitive. ^[19]

Pathway

Viscerosensory information is relayed from the periphery by afferent fibers in sympathetic and parasympathetic nerves. Nociceptive afferents from thoracic and abdominal viscera travel along the path of visceral sympathetic efferent fibers. Thoracic nociceptive afferents travel to the thoracic splanchnics before converging onto the paravertebral sympathetic trunks and then entering the dorsal horn. Abdominal nociceptive afferents travel to the celiac plexus and the thoracic splanchnics prior to entering the sympathetic trunks and dorsal horn. In contrast, the pelvic visceral nociceptor afferents converge on the pelvic splanchnic nerves, which are primarily parasympathetic efferent fibers. Some pelvic afferents also pass through the lumbar sympathetic splanchnic nerves. On entering the dorsal horn, visceral afferents terminate on spinal cord lamina I and V. Visceral afferents constitute 10% of all afferent inflow into the spinal cord. This is a relatively small number when considering the large surface area of some organs. However, the number of dorsal horn neurons that respond to visceral stimulation is estimated to be 56% to 75%, suggesting functional divergence of these neurons. There are no neurons that respond exclusively to visceral afferents. Both anatomic and electrophysiologic studies have demonstrated viscerosomatic convergence in both the dorsal horn and supraspinal center. There is also evidence of viscerovisceral convergence onto these second-order neurons. Examples include the convergence of pelvic visceral inputs such as colon/rectum, bladder,

uterine cervix, and vagina. Poorly localized visceral pain may be explained by the low density of visceral nociceptors, the functional divergence of visceral input with the central nervous system, and viscerovisceral convergence in the spinal cord. In addition to the spinothalamic and spinoreticular tracts, three new pain pathways have been identified in the spinal cord — the dorsal column pathway, the spinoparabrachioamygdaloid pathway, and the spinohypothalamic pathway. The dorsal column pathway differs from the spinothalamic neurons in that it ascends ipsilaterally near the midline before terminating in the nucleus gracilis. From there, internal arcuate fibers transmit nociceptive input to the ventroposterolateral (VPL) nucleus of the thalamus. Recent work by Al-Chaer and colleagues has identified the dorsal column as being more important in visceral nociceptive transmission than the spinothalamic and spinoreticular tracts. In monkeys, colorectal distension stimulates firing of viscerosensitive (VPL) neurons. After a dorsal column lesion at T10 level, the responses were dramatically reduced despite ongoing stimulation. Interestingly, a similar lesion of the SPT at T10 does not achieve the same effect. Further animal studies have recently reported that the dorsal column also has a role in signaling epigastric nociception. These newly identified pathways have led to new clinical approaches in managing visceral cancer pain. In humans, midline myelotomy has been used to treat visceral pain. Its success is clearly not due to interruption of the decussating fibers of the SPT, as was previously thought. This procedure has been performed successfully for pelvic cancer pain and did not produce neurological sequelae.^{[16][17]}

- **Referred Pain**

Visceral pain may be localized to distant and often superficial somatic structures such as muscle or skin. A common example of referred pain is the shoulder, abdominal, and back pain that occurs with pancreatic carcinoma. Viscerosomatic convergence provides a convincing explanation for “referred pain.” This “convergence-projection” theory proposes that the activity in ascending spinal pathways is misconstrued as originating in somatic structures because of previous experiences of somatic pain. When somatic structures are invaded by visceral malignancies, further localized pain may ensue. Local hyperalgesia may occur at the referral site. This may be due to a combination of central sensitization as a result of continual noxious visceral input and peripheral algogenic

mechanism. managed by neurolysis of the superior hypogastric plexus, while perineal pain due to pelvic cancer can be eased by blockade of the ganglion impar. Ablative neurosurgical techniques are used less often than in the past, but for patients with refractory unilateral cancer pain, percutaneous cordotomy may still be useful. The recently described dorsal column pathway may also offer therapeutic options for the future.^{[16][24]}

• **Neuropathic Cancer Pain**

Neuropathic pain results from damage or inflammation of the nervous system, either peripheral or central. Only peripheral neuropathic pain will be discussed here. In patients with cancer, peripheral neuropathic pain can be caused directly by infiltration or compression of the nerve by the tumor or indirectly by cancer treatments such as radiation therapy and chemotherapy (eg, vincristine). In debilitated patients, herpes zoster is common, and post-herpetic neuralgia may follow. Neuropathic pain is characterized by the following pain symptoms: spontaneous burning pain with an intermittent sharp stabbing or lancinating character, an increased pain response to noxious stimuli (hyperalgesia), and pain elicited by nonnoxious stimuli (allodynia). The relationship between mechanism and symptomatology is complex. The underlying mechanism can be different for the same symptom, while the same mechanism can result in different symptoms. Neuropathic pain is generally described as burning or electrical in nature. This type of pain is due to neuronal injury either by the effects of treatment or by tumor invasion. For example, cisplatin, vincristine, and procarbazine can be harmful to nerves. Neuropathic pain may not always be responsive to opioid therapy. Patients with neuropathic pain may report discomfort provoked by a stimulus that does not normally cause pain, such as light touch. Neuropathic pain may have a corresponding neurological deficit

Mechanisms of Neuropathic Pain

Spontaneous firing of C-fiber nociceptors and lowthreshold A delta-fiber mechanoreceptors has been reported after nerve injury in humans. Following nerve injury, sodium channels accumulate both at the site of injury and along the length of the axon. These sodium channels form foci of hyperexcitability that result in ectopic action potential discharge in the axon and cell body of the nerve fiber. Sympathetic activity also plays a role in the mechanism of spontaneous pain. Expression of beta-adrenoreceptor in injured and uninjured axons can occur after nerve injury,

rendering them sensitive to circulating catecholamines. Nerve injury can induce growth of sympathetic axons around the sensory neurons in the dorsal root ganglion. Dorsal horn neurons act as the “gate-keepers” for nociceptive transmission, receiving both excitatory input from sensory neurons and inhibitory input from the spinal cord and higher centers. Peripheral nerve injury may reduce inhibitory control over dorsal horn neurons through various mechanisms. This may result in spontaneous firing of dorsal horn neurons or an exaggerated response to the noxious stimuli. Central sensitization is an important mechanism of hyperalgesia and allodynia. The mechanism has been discussed in the previous section. The resultant effects will be expansion of the peripheral receptor field where a stimulus will activate neurons, increased response to a noxious stimulus, and initiation of action potential discharge from subthreshold input. There are two additional mechanisms for allodynia. Peripheral nerve injury can induce sprouting of A delta- fiber central terminal into lamina II, which normally receives only nociceptive information from C fibers. As a result, the low-threshold information from large A delta afferents that is normally perceived as touch may now be misinterpreted by the nervous system as pain. Peripheral nerve injury can also result in expression of neuropeptides usually involved in nociception such as substance P and calcitonin-gene-related peptide in A delta fiber, a phenomenon called phenotypic switch. Thus, A delta fibers, upon stimulation by low-threshold stimuli, will release substance P in the dorsal horn and thereby generate a state of central hyperexcitability normally produced only by nociceptive input.^{[16][17][24]}

Assessment

Comprehensive pain assessment is one of the most important initial steps for successful management of cancer pain. It is recommended that pain should be evaluated at every clinical visit and incorporated as the “fifth vital sign”. Ideally, the assessment should target the severity, duration, quality, and location of the pain. Reports of pain made by the patients should be the primary source of pain assessment and should be obtained at periodic intervals. The cornerstone of adequate pain management is a thorough patients assessment and frequent reassessment. A complete history and a physical examination, with emphasis on the patients symptoms, are obtained, including information regarding the location, intensity, radiation, aggravating factors, timing, quality, and meaning of the pain.

Medications and treatments are reviewed, and a psychosocial history is taken. The management of cancer pain depends on a comprehensive assessment that characterizes the symptom in terms of phenomenology and pathogenesis, assesses the relation between the pain and the disease, and clarifies the impact of the pain and comorbid conditions on the patient's quality of life. This assessment requires the use of a standard nomenclature and an approach that explores the many dimensions of pain and other features of cancer. In addition, it is important for the clinician to inquire about how the pain has affected patient's daily activities and relationships with others. Clinicians should attempt to obtain more information about the pain by conducting pain histories to determine a cause and the best treatment modality. It has also been suggested that clinicians pay more attention to psychological factors because fear and anxiety may have significant effect on the perception and experience of pain. To help introduce objectivity in the evaluation, a number of pain scales have been utilized to quantify pain intensity. Currently, it is recommended that pain should be measured using a numerical rating scales (from 0–10, where 0 indicating no pain and a 10 indicating the worst imaginable pain). In cases of children, the elderly, and patients with language differences, facial expression scales, i.e, Wong-Baker scale, should be considered. This enables clinicians to make a continuous objective assessment of pain intensity throughout the course of the treatment. To assess the quality of the painful stimulus, it is best to allow the patients to describe the pain themselves, which very often helps healthcare practitioners get a better understanding of the source and the type of pain.^[22]

- **Parameters consider during cancer pain assessment:**

Intensity: The intensity or severity of the pain must first be quantified. Pain rating scales that have been used for more than a decade allow patients to quantify their pain so that health care providers can determine the effectiveness of the therapy. The most commonly used is the numeric rating scale. Pain is rated on a scale of 0-10, with 8-10 being severe pain, 4-7 moderate pain, and 1-3 mild pain.⁶ Other scales, including the visual analog scale and the verbal rating scale, are available to quantify the patient's pain. Each of these scales has specific advantages in helping patients to effectively communicate the intensity of their pain. Once the patients are receiving therapy, pain can be tracked by utilizing the pain scale. This approach also allows the patients to objectively evaluate the efficacy of the

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therapy. The occurrence of severe pain and the frequency in which breakthrough medications are used should be closely monitored. Reliance on breakthrough medication throughout the course of the day should alert the clinician that the patient's therapy needs to be altered. Since most patients have variable tolerances to pain, patients should frequently be asked if the pain is interfering with their daily activities. As some patients are unwilling to admit to having increased pain because this may be associated with progression of their underlying disease, this question often provides insight into the level of pain.^{[21][22]}

Location: Precisely locating the discomfort can also help in determining the type and nature of the pain. Well-localized pain that does not radiate may be somatic in nature and be indicative of metastatic disease to the bone. Pain that follows a dermatomal distribution may be neuropathic in nature and may represent a radiculopathy. Poorly localized, deep pain may be visceral in nature. Asking the patients to mark on a body outline to demonstrate the location of the pain will help the clinician to determine the type of pain that the patient is experiencing.^{[22][23]}

Aggravating/Relieving Factors: Factors that increase or decrease the intensity of the pain can aid in the management of the patient's symptoms and reveal the efficacy of treatment. Pain that increases with movement, especially if an extremity is involved, often signifies bony involvement of that limb. Pain that intensifies in the recumbent position may mean involvement of the spine, and prompt action should be undertaken. Pain that worsens with a light touch is known as allodynia and may be consistent with neuropathic pain.^{[22][24]}

Quality: Patients should be offered a list of adjectives to describe their pain. Pain that is described as burning, shooting, electrical, "pins and needles," and often constant in nature is typically neuropathic. Somatic pain is often described as sharp, aching, constant, well localized, and worse with movement. Visceral pain can be deep, lancinating, episodic, colicky, and often poorly localized.^[22]

Timing: Pain that increases or intensifies at certain times of the day generally indicates that the medication dosage is inadequate. More frequent use or changing to longer-acting medications should be considered.^[22]

Radiation: Pain that radiates over dermatomal or nerve distributions can help in localizing the tumor or provide insight into the type of the pain.^[22]

Meaning of the Pain: Many patients regard an increase in pain as a sign that their disease is progressing or that uncontrolled pain is inevitable. This can lead to feelings of despair and hopelessness. These patients need reassurance that their pain can be controlled and that their quality of life can be maintained. Below describes a thorough pain assessment in a patient with advanced disease. All patients should complete a standardized questionnaire or undergo a structured interview. The key to good pain management in patients with advanced disease is thorough and frequent assessment. The entire palliative care team can be useful in monitoring a patient's pain. Palliative care nurses are well trained in evaluating the patient's pain. A recent report revealed that referring physicians were satisfied with the performances of hospice nurses in pain assessment and the recommendations offered by the nurses for pain control. Frequent reassessment by nurses allows the practitioner to make management decisions quickly, thus resulting in rapid interventions in the management of the patient's pain. Patients are often unable to adequately rate their pain, and it may be necessary to monitor behavior that could be indicative of pain in some patients. Behavior such as mood swings, agitation, restlessness, and increased fatigue may all signify an increase in the patient's pain. Frequent and thorough reassessment by nurses trained in palliative care who may recognize subtle behavior changes can greatly enhance symptom management. Realistic goals should be set with the patient and family regarding expectations of effective pain management. ^{[22][25]}

- **Commonly Used Pain Intensity Measurement Scales**

Pain Intensity Scales are used to determine the intensity of a patient's pain, both when pain is initially assessed, and over time. Pain Scales are typically designed using either numerical, visual or verbal forms. Some are a combination of one or more of these forms.

Numeric Rating Scale

The Numeric Rating Scale (NRS) is perhaps the most commonly-used pain intensity scale (**fig-2**). Patients are asked to rate the intensity of their pain using a 0-to-10 scale on which 0 equals no pain and 10 represents the worst possible pain.

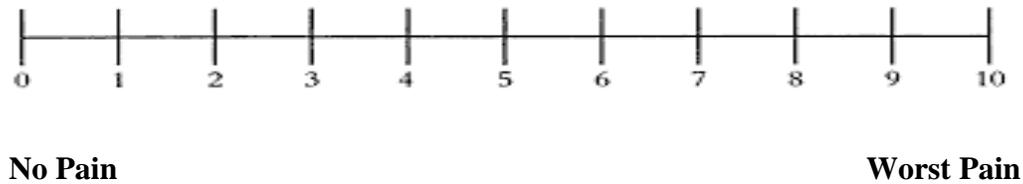


Figure: 2 - Numeric Rating Scale

Verbal descriptor scale

When using a Verbal Descriptor Scale, patients are asked to rate the intensity of their pain using a scale of descriptive words. Scale descriptions range from no pain to excruciating, or as bad as it could be, pain.

- Pain as bad as it could be
- Extreme pain
- Severe pain
- Moderate pain
- Slight pain
- No pain

Faces pain rating scale

When working with patients who have a language barrier and no translator available, or patients with decreased orientation, you might want to use the Faces Pain Rating Scale (**fig-3**), shown here. When using the Faces Pain Rating Scale make sure to have the patient point out which face represents their pain, rather than just looking at the patient's face and deciding on your own.

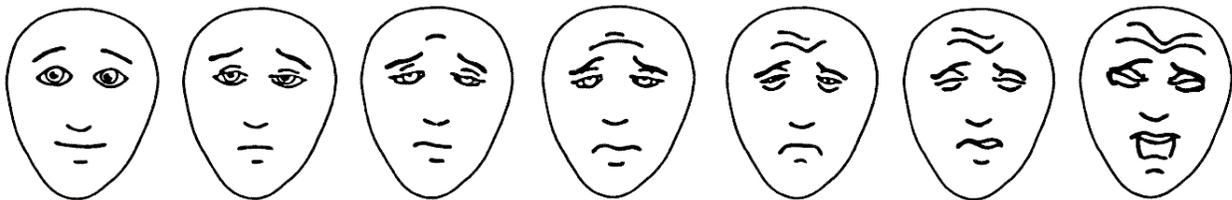


Figure: 3 - Faces pain rating scale

Cancer Pain Management

Symptom control in the home setting may differ from that provided in a more traditional setting such as a hospital or nursing home. In the home setting, the patients or family members provide much or most of the care. The caregivers administer the medications and report changes in the patients status to the health care team. Although the health care team may visit frequently, the patient is dependent on family members for care, which necessitates good communication between the family and the health care team. Pain management must be responsive to the patient's changing symptoms, and care must be taken to respect the family's wishes and limitations. Family members are often reluctant to give injections or administer medicines rectally. Breakthrough medications are often withheld for fear of getting their loved one "addicted" to opioids. Patients may be faced with either financial problems or the lack of an adequate caregiver. For these reasons, the patient's support system and environment must be evaluated. The members of the health care team must establish good lines of communication and trust with their patients and the patients' families, and they must recognize the limitations that may be present in each home. In recognizing the need for improved pain management worldwide, the World Health Organization (WHO) instituted a three-step analgesic ladder as a basis for pain management.^[22]

Step 1 - Mild Pain: acetaminophen or NSAID +/- adjuvant.

Step 2 - Mild to Moderate: weaker opioid for mild to moderate pain + acetaminophen or NSAID +/- adjuvant.

Step 3 - Moderate to Severe Pain: stronger opioid for moderate to severe pain + acetaminophen or NSAID +/- adjuvant.

The WHO also recommended that in the relief of cancer pain, medication be given according to the following framework:^[22]

By Mouth: Oral administration of medication is an effective and inexpensive method of medicating patients and should be used when possible. Medicines are easy to titrate using this route and are therefore the preferred method of administration.

Around the Clock: Patients should receive their pain medicines throughout the day either by routine administration or by sustained release preparations. This allows for continuous pain relief and minimizes the episodes of pain the patient may suffer throughout a 24-hour period. The goal is to prevent pain rather than react to pain.

By the Ladder: The types of pain medications should be changed according to the severity of the pain, using the WHO stepwise approach as a guide to maximize pain relief.

On an Individual Basis: Each patient should be treated individually. Patients may require different dosages and/or interventions in order to attain good symptom relief.

With Attention to Detail: Patients need to be closely monitored for the efficacy of the intervention and the appearance of side effects during therapy. The WHO has taken the initiative to advocate aggressive treatment of pain. It has recommended to practitioners that regimens be individualized for each patient and that pain generally can be well controlled by the appropriate use of opioids. The National Comprehensive Cancer Network recently released practice guidelines for cancer pain. While stressing the importance of a comprehensive pain assessment and ongoing reassessment, these guidelines recommend specific medications and doses dependent on the severity of pain. For both moderate and severe pain, short-acting opioids are recommended for initial titration. Guidelines for the appropriate length of time for follow-up reassessment as well as the recommended dosage changes are also provided. In addition, comprehensive treatment including educational activities and psychosocial support is recommended. The prevention of side effects is also stressed. Although these guidelines have yet to be validated, they appear more medication specific and clearer recommendations at varying pain levels.^[22]

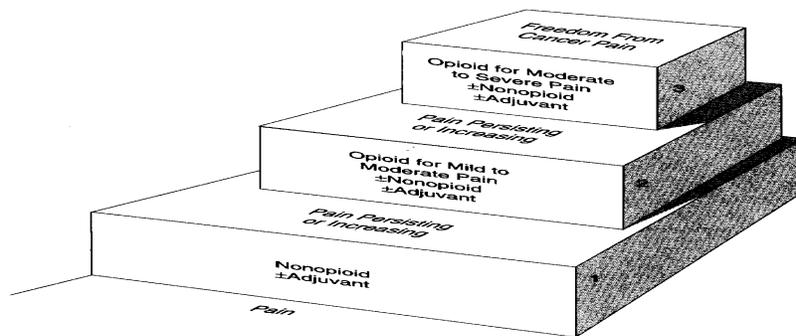


Figure: 4 -WHO ladder for cancer pain management

• **Pharmacological management of cancer pain:**

According to WHO cancer pain treatment ladder (**fig-4**) the initial step in any pain management is consisted of using nonopioid analgesics, which include acetaminophen, aspirin, NSAIDs, such as ibuprofen or ketorolac, and the most recent addition, the selective cyclooxygenase type 2 (COX-2) inhibitors, such as rofecoxib, celecoxib and valdecoxib.

Acetaminophen (paracetamol) is recommended as a first step analgesic for mild to moderate pain. Although its mechanism of action is not fully understood, it is thought to inhibit central prostaglandin synthesis in the central nervous system, which explains its analgesic and antipyretic activity without any effects on inflammation. Acetaminophen is not generally used alone for cancer pain, but rather in combination with opioids (ie, hydrocodone, codeine, etc) Although acetaminophen is effective and well tolerated by most of the patients, its use is limited by a maximum daily dose of 4000 mg (2000 mg/day in patients with hepatic dysfunction) due to potential hepatic toxicity. On the other hand, the gastro-intestinal toxicities seen with chronic NSAIDs use are not seen with acetaminophen. Acetaminophen is excreted by kidneys and dosing must be adjusted in patients with significant renal insufficiency. Aspirin is another drug from this group that can be used for mild to moderate pain control. Unlike acetaminophen, aspirin serves not only as an analgesic and antipyretic but also as an anti-inflammatory agent, which may be an important addition to the therapeutic effect in patients who have severe inflammatory pain. It is a safe over-the-counter drug widely used for noncancerous acute pain control and for

management and prophylaxis of myocardial infarction due to its well-established anti-platelet action. However, it has to be used very cautiously in cancer patients, as in high doses required for adequate pain control (650–1000 mg orally every 4–6 hours) aspirin can cause a number of unwanted side effects, such as tinnitus, vertigo, hyperventilation, as well as increased risk of peptic ulcer disease and gastrointestinal (GI) bleedings. If overdosed, aspirin can cause cardiovascular instability, exacerbate underlying renal insufficiency, and even lead to coma with renal failure, metabolic acidosis, and respiratory arrest. NSAIDs are potent analgesics, antipyretics, and antiinflammatory agents, which makes them useful for cancer related pain of musculoskeletal origin. They work

through nonspecific inhibition of cyclooxygenase (COX), an enzyme that mediates prostaglandin synthesis from arachidonic acid. Because of nonspecific inhibition of both isoenzymes of cyclooxygenase (COX-1 and COX-2), all nonselective NSAIDs have significant adverse effects on gastric mucosa and renal parenchyma, and some inhibit platelet function. With chronic use, they can cause serious gastric ulcerations and bleeding, which is a result of the inhibition of COX-1 iso enzyme. Therefore, NSAIDs may not be an optimal choice in patients who are experiencing nausea and vomiting associated with receiving chemotherapy or who have a history of GI bleeding in the past. In addition, care must be taken in patients that may already have renal insufficiency related to advanced age or disease progression because of the potential to exacerbate these conditions due to modulation of prostaglandin activity on renal blood flow (Dunn 1984). The NSAIDs have maximum daily doses that limit their utility in moderate to severe cancer pain management. All of the NSAIDs are available orally, but only ketorolac is available in parenteral form for pain control. Indomethacin, like aspirin, is available in suppository forms for rectal administration.^[32]

COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib) have less potential for GI and hematological side effects seen with the traditional NSAIDs, a factor that makes them more attractive for cancer pain management. These drugs specifically inhibit the COX-2 isoenzyme, which is considered the inducible isoenzyme during painful stimuli. This selectivity spares the inhibition of COX-1, which is thought to be constitutive in the GI tract and required for normal gastrointestinal function. In addition, there are emerging studies that show an antitumoral effect with these agents due to inhibition of cytokine production seen in many solid tumors. This class of drugs is an attractive option in those patients with cancer involving inflammation and those who are at high risk for GI bleeding or platelet dysfunction. COX-2 inhibitors may also be considered as one of the most effective agents for patients with bone metastasis as prostaglandins appear to play an important role in pathogenesis of bone pain. In addition smaller doses of opioids can be used with COX-2 inhibitors thereby minimizing potential risk for opioid side effects. Because of their relatively short half-lives, they are also capable of treating breakthrough pain.^{[25][32]}

Tramadol is a centrally acting nonopiate analgesic with low affinity for μ -opioid receptors, and is effective in the treatment of moderate to severe pain. It has been also shown to inhibit reuptake of serotonin and norepinephrine,

which synergistically enhances its weak opioid mechanism of action. This may explain the reduced incidences of abuse, respiratory depression and other adverse effects of traditional opioids in patients on long-term tramadol therapy. Tramadol can be beneficial in patients who fail nonopioid therapy and wish to delay taking opioids avoiding the common side effects of constipation, somnolence, and fatigue. It is shown to be effective in such nonmalignant opioid-resistant chronic pain states as fibromyalgia and diabetic neuropathy, and had marginal to moderate success in the treatment of chronic cancer pain. Unlike the NSAIDs, tramadol has no anti-inflammatory activity, extensively metabolized in the liver and is available in tablet form only. As pain progresses, nonopioid regimens alone may not be sufficient to provide necessary analgesia or may be approaching maximum recommended daily doses. At this point, a trial of opioid and nonopioid analgesic combination may be instituted. A variety of fixed combinations with acetaminophen are available on the market, which usually include codeine, hydrocodone, oxycodone, or propoxyphene. Based on extensive evidence of their efficacy, these combinations are recommended in the second step of WHO analgesic ladder for the management of moderate to severe pain. Another attractive choice for long-term pain treatment is the combination of acetaminophen with tramadol, which has been demonstrated in humans to be more effective with a faster onset and longer duration of action than either component alone, without increasing the incidence of adverse events. The opioids are typically the most common drug class used in the treatment of cancer pain. They work by binding to μ -opioid receptors within the central nervous system, which are responsible for opioid-mediated analgesia, respiratory depression, sedation, physiological dependence, and tolerance. Analgesic effect of opioids is largely dependent on μ -receptor saturation and is thus influenced by the type and severity of the pain, prior exposure to opioids, and individual distribution of receptors. There is no maximum dose for these agents; they are only limited by the development of side effects that are patient specific in their onset and severity. Common opioid side effects include nausea, constipation, sedation, and confusion, and they can be often managed without compromising pain control by adjusting the daily dose of the drug or in persistent cases by instituting additional medications, such as metoclopramide for nausea, laxatives for constipation, or methylphenidate for sedation. Prolonged use of opioids may lead to development of tolerance (the need to increase

opioid dose with time to maintain equipotent analgesic effects) and opioid-induced abnormal hypersensitivity to pain (so-called pro-nociceptive sensitization). Experimental studies suggest that both phenomena could be related to N-methyl-D-aspartate (NMDA) receptor mediated changes in central nervous system. Opioid desensitization and hypersensitization of NMDA receptors from prolonged opioid therapy may both contribute to an apparent decrease in analgesic efficacy, regardless of the progression of the pain. Thus, in some instances, treating increasing pain with increasing doses of same opioid may be futile. Although this has not been shown conclusively in the clinical setting, NMDA receptor antagonists (ketamine, dextromethorphan, memantine, amantadine) and low-dose opioid antagonists (naloxone, naltrexone) might partially reverse opioid tolerance. In addition, because the cross-tolerance to opioids is incomplete, opioid rotation (switching from one opioid to another) can be also used to overcome the unwanted adverse effects of opioid receptor desensitization.^[32]

Morphine is considered the standard opiate and the drug of first choice in the treatment of moderate to severe cancer pain. It should be titrated to maximum tolerability before moving on to another opiate such as fentanyl, hydromorphone, or oxycodone. Morphine, is available in a variety of formulations (ie, parenteral, oral, rectal) and the oral form is available in a range of preparations, from immediate release to sustained release, allowing it to be precisely titrated to the patient's response. The oral formulation is recommended initially due to its ease of administration and convenience of use. A typical regimen consists of a sustained-release (SR) preparation given every 8–12 hours with breakthrough doses of immediate-release (IR) form given every 3–4 hours in between if needed. As a guide, the cumulative as-needed doses should not exceed the total dose given as a sustained preparation for that interval. Thus, a patient requiring morphine 120 mg SR every 12 hours should receive morphine 30 mg IR every 3 hours for breakthrough pain. The most common adverse effects of morphine include sedation and some degree of cognitive impairment, which usually improves with time in patients taking stable and moderate doses of opioid. Nausea and vomiting are frequently seen upon initiation of therapy and after large dose increases, but usually subside with time. Constipation is seen with chronic therapy; patients do not develop tolerance to it and typically require preemptive treatment with laxatives. One of the important aspects to consider for adequate opioid treatment

is that patients may have varying responses to an individual opioid based on various pharmacodynamic and pharmacokinetic interactions. For example, morphine is hepatically glucuronidated to two metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G has no analgesic properties but may be involved in certain side effects such as myoclonus. M6G is a more potent analgesic than the parent compound and passes much more readily into the central nervous system. Morphine and its metabolites are excreted by the kidneys and toxicity can be seen in patients with underlying renal insufficiency or failure.^{[26]-[31]}

Fentanyl is a quick acting lipophilic opiate available in parenteral, transmucosal, and transdermal formulations. Intravenous fentanyl is 70 to 100 times more potent than IV morphine and has very rapid onset of action – 5 minutes to peak analgesia, versus at least 15 minutes for IV morphine. Fentanyl is most widely used in palliative medicine in the form of a transdermal patch (Duragesic®), which is especially useful in those patients who do not have enteral access for analgesia or for whom nausea and vomiting limit the ingestion of the required dose of opioid. The efficacy and tolerability of transdermal fentanyl for long-term treatment of cancer pain have been extensively studied and very well documented. The release of fentanyl from the transdermal system is characterized by two distinct phases following initial application: during the first phase, a rapid loading dose is absorbed from the contact adhesive, which is followed by a plateau phase when fentanyl is released from the patch reservoir at a constant rate. Although it may take 12–24 hours for the initial onset of action to occur (Korte et al 1996), transdermal route eliminates gastrointestinal absorption and subsequently first-pass metabolism of fentanyl, which makes possible to use lower doses of medication and reduce incident of adverse effects. One of the main drawbacks of transdermal fentanyl is that its elimination half-life is up to 18 hours after patch removal, thus patients who experience side effects, especially respiratory depression, will need to be monitored and supported for a full day following discontinuation.^{[26]-[31]}

Oxycodone is a synthetic opioid that is metabolized hepatically to the active oxymorphone. One study compared controlled-release oxycodone and morphine tablets in 45 cancer patients, and although the authors found that both drugs have provided similar analgesic effects, there were differences in pain relief in those patients who had

underlying renal or hepatic dysfunction with better pain control in patients receiving oxycodone. This may be due to the accumulation of active metabolites or differences in the phenotype for CYP2D6 that metabolizes oxycodone. In most markets, oxycodone is significantly more expensive than morphine and is thus less attractive as a first-line analgesic. CR oxycodone (Oxycontin®), based on special drug delivery system known as AcroContin system, uses a dual-control matrix with two hydrophobic polymers, which are not influenced by pH and therefore are independent of acidity. Oxycontin® is effective in moderate to severe cancer pain and allows for convenience of every 12 hours administration. [26]-[31]

Methadone is an inexpensive synthetic opioid agonist that has a very long half-life, no active metabolites, and little tendency to induce tolerance in patients. It has unique properties that make it useful in treating pain which is poorly controlled by other opioids. In addition to binding to the opioid μ -receptor, methadone produces analgesic effects through its antagonism at the NMDA receptor site and by increasing the availability of neurotransmitters serotonin and norepinephrine within the central nervous system. Methadone works particularly well in opioid rotation and may be an effective alternative for cancer patients. [26]-[31]

Ketamine also has effects in blocking the NMDA receptors and has found some success in treating neuropathic pain, especially in a situation where large doses of opioids have contributed to the development of severe hyperalgesia. Ketamine can be given by multiple routes: IV, IM, SC, oral, rectal, nasal, transdermal, epidural, or even Intrathecal. Ketamine has been used in a variety of neuropathic pain syndromes that are refractory to high-dose opioids, such as central pain, ischemic pain, and pain associated with posttraumatic nerve or spinal cord injury, as well as in fibromyalgia, refractory facial pain, and post-herpetic neuralgia. [25][33]

- **Adjuvant analgesics:**

The term “adjuvant analgesic” describes any drug with a primary indication other than pain, but with analgesic properties in some painful conditions. They can be added to the regimen at any time depending on the quality of the pain. In some cases, the type of pain suggests the value of one category of adjuvant analgesic over another; in others, the existence of another symptom concurrent with pain favors the use of a specific drug. There are several major

groups of adjuvant analgesics (ie, antidepressants, antiepileptic drugs, muscle relaxants, corticosteroids, etc) that are used nowadays to intensify the effect of opioids and NSAIDs on long-term pain control. For example, pain that is neuropathic in nature is typically not amenable to standard opiate therapy, and the addition of tricyclic antidepressants (TCA) or/and antiepileptic drugs (AED) can offer a very effective treatment strategy in such patients.

Antidepressants:

Tricyclic antidepressants such as amitriptyline, imipramine, doxepin, and clomipramine are attractive adjuvant agents in cancer patients due to their positive effects on mood and sleep. The analgesic properties of TCA have been extensively studied in a variety of chronic nonmalignant pain conditions. Early use of antidepressants is also justified when pain is accompanied by depression, which is fairly common in patients with advanced cancer. However, the use of TCA, especially in medically ill or elderly patients may be limited due to frequent side effects similar to those seen with opiates, which include drowsiness, constipation, urinary retention, and dry mouth, as well as such serious adverse effects as orthostatic hypotension, liver function impairment and cardiotoxicity. ^{[25][32]}

Nontricyclic compounds, such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI), are generally safer, have fewer side effects than TCA and, therefore, may be considered for patients who have relative contraindications to tricyclics or have experienced severe adverse effects during the treatment. However, there are only limited data supporting the analgesic efficacy in nonmalignant pain management of few SSRI, ie, paroxetine and citalopram, and SNRI, ie, venlafaxine and desvenlafaxine, and no studies have been reported on cancer pain. It is thought that norepinephrine reuptake is necessary for an antidepressant to be effective on neuropathic pain, therefore, TCA and SNRI in general may have better results on alleviating neuropathic pain than SSRI. ^{[25][32]}

Antiepileptics:

There is good evidence that antiepileptics are particularly useful as adjuvant therapy in the long-term management of neuropathic pain. gabapentin (Neurontin) is probably the most widely prescribed medication for the treatment of

cancer related neuropathic pain although its specific mechanism of action has not been fully elucidated at this time. Nonetheless, due to its proven analgesic effects, good tolerability, and a rarity of drug-drug interactions, gabapentin is now recommended as a first-line agent for the treatment of neuropathic pain of diverse etiologies, especially in the medically ill population. It should be initiated at a daily dose of 100–300 mg and can be increased every 3 days. The usual maximum dose is 3600 mg daily, but can be higher if needed, and an adequate trial should include 1–2 weeks at the maximum-tolerable dose. Gabapentin is usually well tolerated, and the most common side effects are somnolence, dizziness, and unsteadiness, which are typically not severe if carefully titrated. There are several other antiepileptics, such as carbamazepine, phenytoin, lamotrigine, pregabalin, and levetiracetam that have been reported to be efficacious in alleviating different neuropathic pain syndromes including cancer-related pain. ^{[25][32]}

Corticosteroids:

Corticosteroids belong to another major group of medications widely used as an adjuvant therapy for cancer-related pain syndromes, which include bone pain, neuropathic pain from infiltration or metastatic compression of neural structures, headache due to increased intracranial pressure and pain due to obstruction of hollow viscous or distention of an organ capsule. They inhibit prostaglandin production, reduce inflammation, decrease capillary permeability, and have membrane stabilization effects, which reduces neuronal excitability. Corticosteroids can also improve appetite, nausea, malaise, and overall quality of life. However, it should be always taken into consideration that corticosteroids when used for a long time can produce significant adverse effects, such as immunosuppression, hypertension, hyperglycemia, gastric ulcers, and psychosis. ^[25]

Other adjunctive strategies may include topical agents (local anesthetics, capsaicin) useful for mucositis or peripheral neuropathies, clonidine, an alpha-2 adrenergic agonist usually given intraspinally (to avoid systemic side effects) for the management of severe intractable cancer pain partly responding to opioids, amantadine, a noncompetitive NMDA antagonist, which has been shown to reduce surgical neuropathic cancer pain, baclofen, which can be used in case of spasticity and central pain secondary to spinal cord lesions, benzodiazepines, which used to reduce patients fear and anxiety related to their disease, as well as antihistamines, antipsychotics, or any

other unusual adjuvant analgesics, that may be beneficial for the treatment of severe refractory pain not responsive to traditionally used drug combinations.^[34]

- **Non pharmacological approaches for pain management:**

Patients suffering from either acute or chronic pain problems may benefit from non pharmacologic measures. These measures may also be combined with pain medication. The guidelines for the management of cancer pain contain a chapter outlining these options. Non pharmacologic interventions are divided into behavioral (psychosocial) interventions and mechanical (physical) interventions. Examples of behavioral interventions include biofeedback, self-hypnosis, and relaxation or imagery training. Examples of mechanical interventions include exercise, cutaneous stimulation, and acupuncture. Behavioral interventions help patients gain a sense of control over their pain management and should be introduced early in the course of their illness. When deciding on the appropriate behavioral intervention, consideration must be given to the intensity of the pain, the expected duration of pain and the patient's mental clarity, past experience with technique, physical ability and desire to employ active or passive techniques. Relaxation techniques are easily taught to patients and include focused breathing, progressive muscle relaxation, music-assisted relaxation, and meditation. These techniques are more useful when combined with pleasant images. The use of physical modalities to manage pain may lead to a decreased requirement for pain-relieving drugs and, just as with behavioral interventions, should begin early in the disease process. Cutaneous stimulation techniques include the application of heat or cold, massage, pressure, and vibration. Exercise techniques should be aimed at preventing immobilization and may include range of motion and stretching. Counter stimulation techniques include the use of transcutaneous electrical nerve stimulation (TENS) devices or acupuncture. These last two techniques have not been formally studied in cancer-related pain.^{[19][21]}

Conclusion

Cancer pain is very severe problem. Many cancer patients have more than one type of pain syndrome and pharmacological therapy is the only way to manage it. The principle of good pain management includes thorough initial assessment and frequent reassessment to monitor the efficacy treatment and overcome onset of side effects.

The majority of cancer patient can attain good pain control with the use of opioids and adjuvant medication. The tolerance, dependence and side effects of drug therapy are much higher while treating cancer pain. As the survival of patients with cancer becomes longer, reliable pain relief is now a high-priority issue that warrants both scientific research and industrial development of new devices and pharmaceutical agents that would make this pain relief complete, safe, and lasting. So, it is important to investigate sophisticated drugs and new techniques for controlling cancer pain.

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