Pain in Gynecological Cancer

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ABSTRACT

The International Association for the Study of Pain defines pain as “unpleasant sensory and emotional experiences associated with actual or potential tissue damage.” Pain is common among patients with cancer, with the prevalence of pain being 66.4% in advanced metastatic disease or terminal, 55% during anticancer treatment, 39.3% after curative treatment, and moderate to severe pain were reported in 38.0% of all patients. Pain is one of the most common and dreaded symptoms in cancer sufferers, but the exact number of cancer patients who experience pain is difficult to determine. There are a wide variety of studies in defining pain and the tools they use to measure the complexity of this symptom. Good or complete pain control can be achieved in 80-90% of cancer patients. Nevertheless, despite major advances in pain control, cancer-related pain continues to be a major public health problem globally.

1. Introduction

Pain is defined as "unpleasant sensory and emotional experiences associated with actual or potential tissue damage, or described in terms of damage". There is no definite way to distinguish between pain that occurs in the absence of tissue damage and pain that results from damaged tissue. In addition to its physiological basis, pain is influenced by psychological factors such as emotions, cognition, and motivation, as well as the individual's social context and spiritual beliefs. Mood, morale, and meaning of pain can modulate the perception of pain for an individual. Pain can sometimes be seen as a test or a challenge, which can change the patient's attitude towards treatment.1-5

The term nociception comes from noci (Latin for harm or injury) and is used to describe the nervous response to traumatic or dangerous stimuli. All perceptions of nociception produce pain, but not all pain results from nociception. Many patients experience pain in the absence of noxious stimuli. It is therefore clinically useful to divide pain into one of two categories: (1) acute pain, which is mainly due to nociception, and (2) chronic pain, which may be due to nociception, but where psychological and behavioral factors often play a role. the main role. Pain can also be classified according to pathophysiology (eg nociceptive or neuropathic pain), etiology (eg arthritis pain or cancer pain), or area affected (eg headache or low back pain). This classification is useful in the choice of treatment modality and drug therapy. Nociceptive pain is caused by activation or sensitization of peripheral nociceptors, specialized receptors for the transduction
Neuropathic pain is pain that results from injury or an acquired abnormality of the peripheral or central nerve structures.

Cancer pain is not a well-defined entity and can be defined differently across studies. An individual may have a number of different pain senses, each with different characteristics. Some pain sensations may be immediate due to tumors and other causes due to treatment (for example, oral mucositis from chemotherapy), and others not related to cancer (for example, joint pain from osteoarthritis). Pain can be acute or chronic. Alternatively, some sources may define cancer pain in terms of its pathology (e.g., nociceptive or neuropathic).

Epidemiology of pain in cancer

It is estimated that 6.6 million people from all over the world die from cancer each year. Pain can occur at any time during the disease. Many people with cancer will visit their health care professional because of pain, which may be the first sign of malignancy. Interventions used to diagnose cancer, including biopsy and other tests, can be painful. Cancer treatment can be associated with both acute and chronic pain. Finally, the disease that gets worse can cause pain. Although pain is a very dreaded symptom associated with all phases of cancer, in most cases pain can be adequately treated.

Estimates of the prevalence of cancer pain vary widely, mainly because of a lack of standardization in the definition of pain and the measures used to assess such pain, and because of the heterogeneity of nociceptive and neuropathic pain conditions. Other factors contributing to the wide variation in outcomes include heterogeneity of cancer diagnosis (breast, lung, etc.) and the type of treatment setting in which the study was conducted (outpatient, inpatient, or community setting). In general, the prevalence of pain at the time of cancer diagnosis and early in the course of the disease is estimated to be 50%, increasing to 75% at an advanced stage. A recent meta-analysis found the prevalence of pain in cancer survivors to be 33%. One strategy for evaluating the prevalence of pain in cancer patients is to consider the following categories: pain associated with cancer, its treatment, or an unrelated cause.

Tumors can hit adjacent tissue, causing pain. Although reports vary widely, the highest reported pain prevalence ranges for the following tumors are

- Head and neck (67–91%)
- Prostate (56–94%)
- Uterus (30–90%)
- Genitourinary (58–90%)
- Breast (40–89%)
- Pancreas (72–85%)

Additionally, treatment-related pain may include peripheral neuropathic pain from chemotherapy agents such as vincristine, platinum, taxanes, thalidomide, bortezomib, and other agents; radiation-induced nerve damage, including radiation-induced brachial plexopathy and post-radiation pelvic pain syndrome; and postoperative pain syndromes resulting from mastectomy, amputation and thoracotomy. People with cancer may experience pain that is not related to cancer, such as peripheral neuropathy due to diabetes or pain after surgery for an unrelated condition.

Pain mechanism

Pain occurs along three nerve pathways that transmit noxious stimuli from the periphery to the cerebral cortex (Figure 1). The primary afferent neuron cell bodies are located at the root of the dorsal ganglia, which are located at the vertebral foramina of each level of the spinal cord. Each neuron has one axon that forks, sending one end to the peripheral tissue that supplies it and the other into the dorsal horn of the spinal cord. In the dorsal horn, primary afferent neurons synapse with second-order neurons whose axons cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus. Second-order neurons synapse in the thalamic nucleus with third-order neurons, which in turn send projections via the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex (Figure 2).
First order neurons

The majority of first-order neurons send their proximal axon ends to the spinal cord via the dorsal (sensory) spinal roots at each cervical, thoracic, lumbar, and sacral level. Several myelinated (C) afferent fibers have been shown to enter the spinal cord via the ventral (motor) nerve roots, taking into account the observation that some patients continue to experience pain even after transection of the dorsal nerve roots (rhizotomy) and pain after ventral root stimulation. Once in the dorsal horn, in addition to synapses with second-order neurons, first-order neuron axons 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 first-order afferent cell bodies of facial nerve neurons are located in the ganglion of the genicu end; from the glossopharyngeal nerves located in the superior and petrosal ganglia; and from the vagal nerves located in the jugular ganglion (somatic) and ganglion nodosum (visceral). The proximal axonal processes of first-order neurons in these ganglia reach the nucleus of the brainstem via their respective cranial nerves, where they synergize with second-order neurons in the nucleus of the brainstem.

Second order neurons

When afferent fibers enter the spinal cord, they separate the gates according to size, with large myelinated fibers becoming medial, and small, unmyelinated fibers becoming lateral. Pain fibers may ascend or descend one to three segments of the spinal cord in the Lissauer tract before synapses with second-order neurons in the ipsilateral dorsal horn gray matter. The gray matter of the spinal cord was divided by Rexed into ten laminae (Figure 3). The first six laminae, which form the dorsal horn, receive all afferent nerve activity and represent the primary site of pain modulation with ascending and descending nerve pathways. Second-order neurons can be either nociceptive-specific dynamics or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only harmful stimuli, but WDR neurons also receive harmless afferent input from Aβ, Aδ, and C fibers. Nociceptive-specific neurons are regulated somatotopically in lamina I and have discrete, somatic receptive fields; they are usually silent and respond only to dangerous stimulation of high threshold, intensity of poor coding stimulus. WDR neurons are the most common cell type in the dorsal horn. Although they are found throughout the back of the horn, WDR neurons are most abundant in lamina V. During repeated stimulation, WDR neurons characteristically increase their activation rate exponentially in wind-ups, even with the same stimulus intensity. They have a large receptive field compared to nociceptive specific neurons.

Third order neurons

Third-order neurons are located in the thalamus and send fibers to the somatosensory areas I and II into the postcentral gyrus of the parietal cortex and the respective superior walls of the sylvian cleft. Perception and discrete localization of pain occurs in the cortical area. Although most of the neurons from the lateral thalamic nucleus project to the primary somatosensory cortex, neurons from the intralaminar nucleus and medial nucleus to the end gyrus of the anterior and are most likely involved in mediating the suffering and emotional components of pain.

The cancer pain mechanism is a complex logical process consisting of cellular, tissue, and systemic changes that occur during cancer proliferation, invasion, and metastasis, in addition to the reciprocal interactions between cancer cells, the peripheral and central nervous systems, and the immune system. The intensity of cancer pain is influenced by the histological type of cancer, the location of the primary neoplasm and its metastases, the stage of the cancer, receiving anticancer therapy, and pain due to coexisting diseases that are not related to cancer and its treatment. The pain felt by the cancer sufferer was also significantly
influenced by psychological and emotional factors (for example, anxiety, depression).6,11

Pain in cancer sufferers is usually caused by several causes:

- The presence of tumors or their appearance and / or metastatic growths
- Anticancer therapy (diagnostic procedures, surgical intervention, radiotherapy, chemotherapy)
- Mechanisms indirectly related to cancer and its treatment (infection, metabolic imbalance, myofascial pain)
- Mechanisms not related to the cancer itself or its treatment (migraine, painful diabetic neuropathy, low back pain)6,11

Several pain mechanisms that directly accompany tumor growth or metastasis can cause pain or exacerbations in cancer patients.6,11

Pain due to tumor growth and development of metastases

Nociceptive pain: somatic pain in cancer patients

This type of pain can be caused by neoplastic invasion of the bones, joints, muscles, or connective tissue. The tumor mass produces and / or stimulates the production of local inflammatory mediators, leading to activation of peripheral nociceptors. Other sources of somatic pain in cancer patients include, reactive muscle spasms in the area of tissue damage caused by cancer, postoperative incision pain, or radiotherapy / chemotherapy pain syndromes (e.g., mucositis, proctitis). This pain can be divided into superficial pain (i.e., skin ulceration with malignant involvement) and deep pain (e.g., bone marrow infiltration by malignant cells, osteitis lesions). Most skin pains are well localized, sharp, or stabbing. Usually deep tissue pain appears to be diffuse.6,11

In somatic structures, tumors develop which directly involve the tissues that trigger the release of potassium ions, ATP, bradykinin, prostanoids, and other combustible mediators that activate nociceptors - "pain receptors" - located at the primary ends of afferent sensory neurons. The main function of nociceptors is to detect chemical or physical stimuli and convert them into electrochemical signals that are transmitted to the central nervous system (CNS) via sensory fibers (myelinated C fibers and myelinated A).6,11

In addition, tissue damage caused by tumor growth (other than orthodromic transmission of nociceptive stimuli to the CNS) induces release of mediators such as substance P (SP) and s fibers from primary afferents A along the antidromic pathway. This tissue damage leads to vascular dilation (increased capillary permeability) which results in tissue edema and release of bradykinin (BK) and serotonin (5-HT) from platelets, histamine from mast cells, other tissue mediators such as prostanoids (PG), nerve growth factors (NGF). These mediators also increase cytokines (TNF-α). These mediators also increase vascular permeability and SP release.6,11

The presence of tumors is accompanied by the production of cytokines with necrosis of immune stimulating tumors (TNF-α factor cells to produce pronociceptive mediators that act on primary afferent fiber nociceptors and directly cause hyperalgesia in cancer.6,11

Bone pain in cancer

Bone pain is the most common type of pain caused by cancer. Bone pain is present in 28-45% of patients with bone metastases. The majority of patients with metastatic bone disease experience moderate to severe pain. The three most common sites of metastasis are the skeleton. Metastasis can also occur in the lungs and liver [affects the bones in 30-69% of cancer patients, especially in patients with advanced breast, lung, and lung cancer]. This syndrome is caused by osteolytic lesions and filtration in the bone marrow by malignant cells. This process causes pain relief by activation of the sensory nerves and sympathetic fibers innervating the periosteum, mineralized bone, and bone marrow. Tumor growth in the bone causes pain, and it may also result from a fracture or compression of the spinal cord. The most common pathology of fractures occurs in patients with myeloma and breast
cancer and affects mainly the vertebral bodies, ribs, and long bones [the most serious complications of vertebral metastasis include compression of the spinal cord caused by vertebral collapse or secondary spinal injury]. The collapse of the impaired vascular supply of the vertebral bodies is a consequence of frequent metastases in the thoracic spine and may lead to compression of the thoracic nerve roots and bilateral radicular pain localized in the chest. In bone metastases characterized by increased osteoblast activity, the lesions appear sclerotic and characteristic.6,13,14

Visceral pain in cancer

Visceral pain is caused by pathological processes that occur in the internal organs in the thorax, abdominal cavity and pelvis. Pain may result from distension, impact, ischemia, inflammation, or traction of the mesentery. The growth of the tumor tissue inside can cause all the mechanisms mentioned above and, as a consequence, cause the onset of pain. Compared with somatic pain, visceral pain is not well localized because both receptors participate less in the visceral pain process and are "rare representations" in the primary somatosensory cortex. The diffuse nature of visceral pain is due to the convergence of visceral and somatic afferents in the same neurons in the dorsal horn of the spinal cord. Convergent receptive fields are generally described as multidermatomal and significantly larger than spinal neuron receptive fields, receiving only somatic input. This observation also explains why visceral pain is difficult to localize and is often referred to as other areas of the body. The viscera are innervated by two distinct classes of nociceptive sensory receptors. The high threshold receptors are activated by stimuli in the noxious range and contribute to the peripheral encoding of harmful events in the viscera. However, low threshold receptors are activated by a range of stimulation intensity from harmless to harmful.6,11

Tumors in certain organs (liver, spleen, kidneys) cause pain due to stretching of the capsule, especially in the case of rapid development of liver tumors, which can lead to multiple increases in the dimensions of the organ many times. This results in a significant increase in intra-organ pressure and stimulation of intracapsular mechanoreceptors. Likewise, distension or traction in the gallbladder causes deep epigastric pain. On the other hand, tumor growth in the spleen or kidneys does not cause pain with an intensity comparable to tumor growth in the liver. Kidney tumors produce pain only when the kidney is almost completely destroyed and the tumor has invaded the pararenal tissue or if it has damaged the renal pelvis. Colic renal pain is usually secondary to urethral obstruction and subsequent distension of the renal pelvis and urethra, as is usually the case with tumors located in the lower abdomen.6,11

Anatomic pain

Pain associated with tumors in the bone structure and nervous system is the most common cause of anatomical pain, other anatomical locations can also cause pain. Tumors in the brain are known to cause headaches, as are metastases to the spinal meninges. Distention of the capsular organs is another well-known cause of tumor-related pain as it occurs when a liver tumor swelling belonging to the Glisson capsule causing abdominal pain. In all of these tests, the main treatment for cancer pain is cancer treatment and any therapy that removes or reduces the size of the tumor.1

Neuropathic pain

Neuropathic pain is defined as pain that arises as a direct result of a lesion or disease affecting the somatosensory system. This type of pain develops if the nervous system is damaged, which, in the case of cancer, can occur due to either tumor on neural filtration, as a result of tumor-related or therapeutic-related toxin activity. The prevalence of pain with a neuropathic mechanism ranged from 18.7 to 21.4% of those recorded. The etiological findings of neuropathic pain in cancer patients indicated that 63% of cases were caused directly by cancer and in 20.3% by cancer treatment. The association of neuropathic pain with cancer is not well known.6,11

Further nerve damage leads to pathological
interactions between the somatic and autonomic systems. This interaction is due to the development of pathological contact points of afferent fibers that deliver b sensations between A and C and tactile fibers and nociceptive A sympathetic fibers, both along the nerve and within the neuroma. In addition, sympathetic fibers grow and envelop the DRG in a basket-like manner. Thus, mutual excitation may occur directly or indirectly by endogenous catecholamines. The aforementioned changes in the proximal part of the damaged nerve cause symptoms. 6,11

Neuropathic pain mechanisms may also occur accompanying the inflammatory process. At the nerve damage site, tissues and vessels release substances such as BK, 5-HT, hydrogen ions, protanoids, NGF, cytokines, and free radicals, which cause a flow of immune cells and transudate plasma and a decrease in threshold excitation at nerve endings that innervate the nerve trunk (nervi nervorum). The inflammatory process can cause neuropathic pain without structural damage to the nerves. In recent years, researchers have underlined the role of glial cell excitation and the increased release of inflammatory cytokines in the development of chronic pain syndrome, both after spinal cord damage and peripheral nerve damage. It is postulated that glial cell excitation causes pain radiating far from the site of damage as well as reflex pain syndrome.6,11

Pain related to cancer therapy

Certain pain syndromes are diagnosed in cancer patients because of treatment modalities including surgery, chemotherapy, and radiation therapy. In most cases, pain is the main symptom. The source is damage to the structures of the peripheral or central nervous system (especially the spinal cord). Occasionally, symptoms such as pain and neurological deficits concomitantly develop with a delay of several weeks or even months, which can cause difficulties in the differential diagnosis of complications of therapy and recurrent illness.6

Persistent post-operative pain (post-surgical neuropathy)

According to Marskey’s current definition, persistent postoperative pain is chronic and pathological pain that develops as a result of previous surgical procedures, is associated with impaired tissue continuity, and lasts for more than 3 months of surgery despite site healing tissue. It has several features of neuropathic pain that result from damage to the peripheral or central nervous system. It should be remembered that especially in cancer patients, psychosocial factors such as anxiety, depression, natural disasters, perception of illness, poor coping strategies, low sense of control, or poor social support may significantly increase the likelihood of developing pain.6

Post radiation pain therapy

Radiotherapy used in the treatment of cancer can cause damage to the CNS structures, which may occur as focal radionecrosis. They are radiation responses that primarily affect the white matter of the brain or spinal cord. It results in necrosis and vascular and axonal injury and loss of oligodendrocytes with gliosis and demyelination. Edema, mass effects, increased intracranial pressure, pain, and cognitive dysfunction. Radiotherapy can cause structural damage to the peripheral nervous system. Typical lesions include the brachial and lumbosacral plexuses. Post-radiation plexopathy is more common in patients who, in addition to radiotherapy, are also receiving irradiation, undergoing chemotherapy.6

Chemotherapy-related pain syndrome

The incidence of cancer due to peripheral neuropathy chemotherapy (CIPN) varies between 3 and 7% in single-agent use cases and up to 38% when using combination drugs. Peripheral neuropathy is a common side effect of various drugs used in chemotherapy such as cisplatin, oxaliplatin, vincristine, paclitaxel, and bortezomib. The treatments used in cancer chemotherapy have well-documented direct and indirect documents of neurotoxic action. They influence the nerve fibers to change the amplitude
of the action potential and conduction velocity. Drugs used in cancer chemotherapy activate membrane ion channels (sodium, calcium, potassium) or receptors (NMDA) on the dorsal root ganglia and dorsal horn neurons to convert environmental cytosolic ions. A special role in cytotoxic chemotherapy is associated with changes in intracellular calcium levels that trigger secondary changes inducing neuropathic pain. Increased intracellular calcium levels, activation of protein kinase C, and production and release of nitric oxide and free radicals all cause cytotoxicity in axons and nerve cell bodies.\(^6\)

The most frequently observed consequence of the neurotoxicity of drugs used in cancer therapy is peripheral neuropathy. Chemotherapy-induced peripheral neuropathy may be very painful. It is a source of patient suffering and also limits the possibilities of treatment with potentially useful anticancer drugs. Cisplatin is an anticancer drug that is widely used for cancer chemotherapy. It is most commonly observed to cause neurotoxic symptoms including sensory neuropathy which initially manifests as pain and paraesthesia in the distal limb. The onset of neuropathy is usually delayed by several weeks from the start of chemotherapy.\(^6\)

**Acute pain associated with cancer management**

It should be underlined that a significant factor that negatively impacts the quality of life of cancer patients is acute pain caused by both diagnostic and therapeutic procedures such as chemotherapy, radiotherapy and surgery, and their generally high intensity causes extreme pain and suffering to the patient. For this reason, medical staff involved in cancer management must remember to alleviate it as an urgent problem.\(^6\)

**Pain is not directly related to cancer and its treatment of infection**

Acute shingles is more likely to occur in cancer patients than in the general population because of the higher incidence of immunosuppression in cancer patients. One to two percent of patients have at least one shingles infection during the course of their illness. Approximately 25-50% of patients develop postherpetic nerve neuralgia after acute infection.\(^6\)

**Muscle-related pain**

Myofascial pain syndrome represents a major cause of muscle-related pain. The mean prevalence of this condition among middle-aged adults (30-60 years) is reported to be 37% in men and 65% in women. In the elderly (> 65 years), the prevalence reaches 85%. Pain like this often occurs in cancer patients. Myofascial pain is a common source of pain in women having surgery for breast cancer. The etiology of pain includes sensory neurosurgical damage, axillary dissection, postoperative complications, radiotherapy and chemotherapy complications, and activation of myofascial trigger points.\(^6\)

**Pain secondary to osteoporosis**

Osteoporosis may be due to the significant bone loss that occurs during glucocorticoid therapy or hypogonadism (eg, androgen deprivation therapy, bilateral orchiectomy) and may result in painful fractures of the hip or vertebrae.\(^6\)

**Pain related wounds / pressure ulcers**

It is estimated that injury occurs in at least one-third of cancer patients at the end of their life. The risk factors for tissue damage and the development of pressure ulcers are similar in that they may expose patients with limited mobility and physical activity to the highest risk of developing pressure ulcers. The pain that accompanies this pathological process is usually exacerbated by an inflammatory process caused by wound infection.\(^6\)

**Pain caused by a mechanism not related to the tumor or its treatment**

Cancer patients, both during active treatment and in the terminal phase of the disease, may suffer pain that has a mechanism not related to the tumor itself or its treatment. Migraines, tension headaches,
osteoarthritis, painful diabetic neuropathy, and low back pain may all be pre-existing or coexist with cancer. However, consideration should be given that in cachectic patients in the late stages of disease, this pain syndrome may have a more significant effect on overall quality of life than the cancer itself.6,11

Clinical presentation and pain assessment

Assessment is essential in characterizing pain and identifying the underlying mechanism, providing a guided decision-making process about medical therapy. A thorough history and clinical examination of pain is essential for pain assessment. Pain characteristics such as intensity, radiation, duration, temporal variation, quality, provocative, and relieving factors are all essential for effective treatment. The use of mnemonics such as SOCRATES is clinically useful, providing a systematic approach to assessing pain characteristics (Site, Onset, Character, Radiation, Associated factors, Timing, Exacerbating / Relieving factors, and Severity). Pain characteristics and patient characteristics relevant to cancer pain are usually used in clinical practice to classify or categorize pain within specific domains.1,15

1. Pain intensity

Intensity is one of the most relevant characteristics of pain, which is also considered the gold standard for pain assessment of pain, which often guides evaluation and treatment options. Different methods are used to measure intensity, with Numerical Rating Scales (NRS) being one of the most frequent. Determining the cut-off points for various levels of pain intensity is important for the assessment of response to treatment and changes in patient status. Several attempts have been made to classify patients according to the intensity of their pain, for both clinical and research purposes. One classification used for these two purposes identifies three categories of pain according to pain severity: mild (NRS 1–4), moderate (5–6), and severe (7–10). However, pain intensity needs to be part of a comprehensive assessment and should always be considered in terms of individual patient characteristics including age, cognitive function, and psychological aspects.1,15

2. Site pain

According to the anatomical location, cancer can invade any body tissue, including the viscera, bone, soft tissue, and nerves. It is not uncommon for oncology patients, especially when associated pain to metastatic cancer, to have more than one pain site and this important information is usually recorded using the body map included in many assessment tools. Information should be gathered regarding all pain sites.1,15

3. Pain syndrome

Taking into account the clinical characteristics of pain in cancer patients, based on the recognition of recurrent clusters of signs and symptoms and the association of pain with cancer, it is possible to determine several clinical entities that consolidate into a specific pain syndrome. Identification of this syndrome can help identify the etiology, prognosis and guide therapeutic interventions. Usually the identification of pain syndromes is based largely on the clinical experience of the clinician, however, over time several attempts to describe the most common set of pain syndromes in patients with cancer pain have been made.1,15

4. Time and temporal variation

Pain is traditionally classified as acute or chronic pain, with chronic pain being considered as persistent or recurring pain that lasts for more than three months. However, when it comes to pain in cancer, given that as the disease progresses as well as tissue damage can develop, it is difficult to distinguish between acute and chronic pain.1,15

Reliable measurement of the severity of pain will help determine therapeutic interventions and evaluate the efficacy of treatment. This is a challenge because pain is a subjective experience that is influenced by psychological, social, cultural and other variables. A clear definition is needed, as pain can be described in terms of tissue damage or bodily or emotional reactions. The numerical rating scale, the Wong-Baker
FACES rating scale, the visual analogue scale (VAS), and the McGill Pain Questionnaire (MPQ) are the most commonly used ratings. On a numerical scale, 0 means no pain and 10 is meant to reflect the most severe possible pain. The Wong-Baker FACES pain scale, designed for children 3 years and over, is useful for patients with difficult communication. The patient is asked to show a variety of facial expressions ranging from a smiling face (painless) to a very unhappy one that expresses the most likely pain. The VAS is a 10 cm horizontal line labeled “painless” on one side and “the most severe pain imaginable” on the other. The patient is asked to mark on this line where the pain intensity is located. The distance from “no pain” to the patient’s sign numerically quantifies pain. VAS is a simple and efficient method that correlates well with other reliable methods. MPQ is a glossary describing symptoms. Unlike other pain assessment methods which assume pain is one dimensional and describing intensity but not quality, the MPQ attempts to define pain in three main dimensions: (1) sensory-discriminative (nociceptive pathways), (2) motivational-affective (reticular and limbic structures), and (3) cognitive-evaluative (cerebral cortex). It contains 20 descriptive word sets divided into four main groups: 10 sensory, 5 affective, 1 evaluative, and 4. The patient selects the set that applies to his or her pain and circles the words in each sequence that best describe the taste pain.

**Pain therapy**

**Pharmacological therapy**

Pain relief as much as possible should be practiced clinically in cancer patients, as it may not be possible to completely relieve pain in all patients. The goal of pain management is to reduce pain to a level that allows the patient an acceptable quality of life. Pain relief benefits must be balanced against the risk of side effects and overdoses that can lead to respiratory depression. The diagnosis of "refractory pain" should not be made too early as it appears that "refractory pain" may simply be due to a lack of access to current pain treatments. Invasive interventions for pain, such as nerve blocks, may not be necessary when pain management guidelines are followed.

Many guidelines discuss appropriate treatments for cancer pain. The National Comprehensive Cancer Network (NCCN) in the US updated its guidelines for adult cancer pain in 2013 and offers recommendations for specific types of cancer. The American Society of Clinical Oncology offers cancer treatment guidelines but does not specifically address cancer pain control. The World Health Organization (WHO) developed the famous WHO Pain Ladder in 1988 to help doctors relieve cancer pain by using strong opioids to treat the most intense form of cancer pain. The use of nonopioid analgesics, namely acetaminophen and various drugs (NSAIDs) is recommended by WHO Pain Ladder, but may not be sufficient as a single therapy for all cases. Effective analgesia may require adjuvant agents, such as anticonvulsants or antidepressants, to treat mixed pain syndrome.

The pain therapy ladder consists mainly of three steps:

a. The first stage. Mild pain: non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants

b. Second stage. Moderate pain: weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics, and with or without adjuvant ingredients

c. Third phase. Severe and persistent pain: strong opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants

In identifying suitable analgesics for patients with cancer, the prescribing physician must consider the efficacy of the agent, tolerability, initiation of action, potential for interaction with other drugs the patient is taking, potential responsibility for abuse, and costs. The ideal therapy should be tailored to the patient’s needs, age, and comorbidities and should be easily titrated as the patient’s pain level changes. Routes of
administration can be especially important in patients with cancer: oral and transdermal agents allow maximum patient independence from the clinical team and transdermal is especially useful in patients with dysphagia. The daily dosage regimen is more precise than the required dosage, which allows for analgesics. Optimally, the dosage should allow the level of severe pain to be reduced with the fewest side effects. For other components of pain, such as neuropathic pain, prescription neuropathic analgesics may be appropriate such as muscle relaxants, corticosteroids, tricyclic antidepressants, anticonvulsants, and neuroleptics. Severe breakthrough through pain or procedural pain (for example, pain caused when changing dressings) can be treated with fast-onset opioids, such as transmucosal fentanyl. When treating cancer pain, it is very important to distinguish between pain associated with an oncological emergency and pain not associated with an emergency. If a patient's pain assessment requires treatment with opioid analgesics, treatment will depend on whether they are opioid naïve (have never taken opioids before), or have previously taken opioids. Opioid-naïve patients and families will need education about opioid agents and should be informed about potential side effects. According to the WHO pain ladder, patients who have never used opioids should be treated first with nonopioids, then with so-called "weak opioids," such as tramadol under trade names such as Fiotram, Tramal, Thramed, Tradosik, Tramadol, Dolatram, Zephalan, Tracedol, Ultrace, Ucetra, Orasic, Analtram or codeine with trademarks such as Codeine: Codikaf, Codipront, Codita; low doses of step III opioids (eg, morphine or oxycodone) should be used instead of codeine or tramadol and then advance by increasing pain intensity, as needed, to high doses of "strong opioids", such as morphine or oxycodone. However, combination therapy may be more suitable for such patients, such as acetaminophen or NSAIDs with trademarks such as Panadol, Naprex, Paramol, Mixagrip Flu, Hufagesic, Paramex SK, Sanmol, Sumagesic, Tempra, Termorex, and Poro in combination with the appropriate amounts. smaller opioids (such as oxycodone plus acetaminophen). The patient's first opioid agent may be a short-acting or long-acting opioid, depending on the temporal nature of the drug to the patient's pain, and should be started in conjunction with the bowel regimen education.16,17,18,19

For outpatient care, it is important to allow adequate time for the nonopioid and opioid analgesic plan to achieve its optimal effect, which may occur for several days or even a week or more. Patient adherence should be emphasized.8,9,11,13

For opioid-experienced patients, patients may be started on short-acting opioids; if pain persists at a level of 4 or higher on an 11-point scale, then the oral dose may be increased by 10% to 20% of the opioids taken in the last 24 hours. Efficacy and pain tolerance (possible side effects) should be assessed after the first hour. If the pain does not change, the dose can be increased by 50% to 100%, then reassessed within one hour. If the pain level decreases to a score of 0 to 3, then the dose stream can be continued for the first 24 hours. If the pain score is 4 to 6, the dose should be repeated and reassessed.8,9,11,13

Opioid rotation or transition from oneopioid to another is sometimes required to increase efficacy, overcome tolerance, or increase tolerability. Opioid conversion is required when switching from parenterally administered drugs to oral drugs. There are many nuances of opioid conversion, so the doctor should consult the appropriate guidelines or refer to a pain specialist. Although methadone is sometimes used for cancer pain, its long and variable half-lives (> 100 hours) require careful attention to avoid side effects due to drug accumulation (see Figure 5 for suggested conversions).16,17,18,19

Nonopioid agents, according to Step I on the WHO pain ladder, can also be used for cancer treatment but have their own safety concerns. Acetaminophen (paracetamol) is associated with hepatotoxicity, and many NSAIDs have been associated with gastrointestinal (GI), kidney, and more recently, cardiovascular toxicity diseases.16,17,18,19

When prescribing opioids, the mode of administration must be considered. Oral opioids are convenient to use on an outpatient basis and are often prescribed, but are not suitable for patients who have
difficulty swallowing or for whom there may be problems with adherence. Severely ill patients who require immediate assistance should be treated with parenteral (subcutaneous or intravenous) opioids or transmucosal products. Transdermal products are suitable for round-the-clock opioid therapy in a wide variety of patients with cancer and are particularly useful for avoiding analgesic gaps, adherence problems and tablet swallowing problems. When converting from oral morphine to parenteral morphine, the general guideline is that one-third of the oral dose will provide an equianalgesic effect, but there is considerable variability between patients, so clinical surveillance required when transitioning to oral morphine has long been considered the "gold standard" for cancer pain. But there may be considerable variability between patients in response. Oxycodone has properties similar to morphine and hydromorphone and is used to treat pain in cancer patients. Buprenorphine is recognized as the only opioid agent that is safe for patients with advanced chronic kidney disease. The evaluations of the main opioid agents appear in Table 2. When taken orally, there was no significant difference between morphine, oxycodone, and hydromorphone; direct or continuous release oral formulations can be used for dose titration. During titration, the patient's analgesia can be supplemented by immediate ("rescue") oral opioid release as needed.8,9,11,13

**Non-pharmacological therapy**

Nonpharmacological or interventional therapy for pain in cancer includes nerve block, vertebroplasty, radiofrequency ablation of painful metastases, transcutaneous electrical nerve stimulation (TENS), massage and acupuncture. Nerve blocks, vertebroplasty, and radiofrequency have not undergone randomized clinical trials in cancer patients so these interventions should be used with caution according to patient needs. TENS is used to treat mild to moderate cancer pain and is used in combination with pharmacological treatments for moderate to severe pain. During treatment, an electric current is moved along the surface of the skin to activate the nerves near the skin at the site of pain, basically with the intention of blocking pain signals. Treatment with TENS is contraindicated for patients with pacemakers and bleeding disorders. Although no randomized controlled trial has proven TENS to be efficacious for cancer pain, uncontrolled trials and case reports suggest TENS may be useful for short- and long-term management of cancer pain. Acupuncture is a method of inserting needles into the skin at specific points that can theoretically alleviate pain by changing the flow of energy in an individual. Specific guidelines have been established for acupuncture use with cancer patients and contraindications include "clotting dysfunction, needle phobia, and intra-cardiac defibrillator". Lastly, several studies have examined the use of massage to treat cancer pain with mixed results. The majority of studies showed short-term pain relief up to 18 hours after massage but did not provide pain relief.1

Practical guidelines for the management of cancer pain include a comprehensive assessment of psychosocial factors. The guidelines suggest that raters collect data along the sensory / physical, affective, cognitive, and behavioral domains. Accordingly, a psychosocial assessment should include the following:

**Sensory / Physical**

- The patient's understanding of the cancer diagnosis
- The meaning of pain for the patient and his or her family
- How pain affects relationships in the patient's family

**Affective**

- The relationship between patient mood and pain
- Current and preexisting affective functioning (ie, anxiety, depression, anger, frustration, hopelessness, etc.)

**Cognitive**

- Cognition (ie, expectations and preconceptions) related to pain management

**Behavior**

- Pre-existing and current coping strategies
- Impact of pain on patient sleep patterns
- Availability of social support
Psychosocial assessments are most often completed through face-to-face interviews with the patient and possibly from one or more members of the patient's family and/or significant others. During these interviews, the mental health clinician collects demographic and clinical information about the patient's background and current situation, and evaluates the psychosocial domain. From oncologists' reports, mental health physicians can gain an understanding of the extent of illness, medical treatment of disease and pain/symptom control, prognosis, and phases of disease timeline. Pain medicine doctors can provide mental health physicians with an understanding of the initial assessment of a patient's pain syndrome and subsequently updated biomedical information.1,21

Clinical practice guidelines issued by the World Health Organization, American Pain Society, and the National Comprehensive Cancer Network (NCCN) recommend both pharmacological and psychosocial interventions to be effective in pain management in patients with cancer. The origin of psychosocial interventions for patients with cancer pain stems from interventions that have been well studied for patients with noncancerous pain syndromes. Often, the standard psychosocial intervention protocols developed and used in research are tailored to meet the specific needs, wants, and resources of an individual patient. Psychosocial interventions for cancer pain fall into two main categories: (1) education and (2) skills training.1,21

Lin and colleagues sought to identify the effectiveness of patient and family long-term cancer pain education programs aimed at reducing barriers to patient and family-supported use of analgesics, as well as the effects of education on adherence and use of prescribed analgesics, pain intensity, and pain disorders for cancer patients. Pain education is based on previous research and consists of a culturally appropriate booklet and uses brief descriptions and illustrations to address problems associated with fatalism, addiction, desire to be good, fear of bothering doctors, disease progression, tolerance, side effects, religious fatalities, isms, and use as needed instructions.1,21

Cognitive-behavioral techniques: distraction, cognitive, and relaxation disorders

The cognitive behavioral approach changes the thoughts and behaviors that contribute to the patient's experience of pain. These techniques can increase the patient's sense of control and intellect by giving the patient coping skills that increase self-efficacy, minimize the potential for negative catastrophes, and enhance a sense of well-being. Research supports patients who have high self-efficacy and perceived pain control often experience decreased pain. Cognitive behavioral interventions for cancer patients undergoing painful procedures and/or treatments may benefit those with chronic cancer pain.1

Mind-body therapy: hypnosis and imagery

Hypnosis

Hypnosis is a formal induction of a state of sustained attention and concentration, reduced peripheral awareness, and openness to suggestions. The five main hypnotic techniques that have been used for the treatment of cancer pain are anesthesia, direct reduction, sensory substitution, displacement, and dissociation. Anesthetic technique refers to hypnotic suggestions that form numb areas of the body and are insensitive to pain. Reduction and direct sensory substitution change the meaning of pain to less importance (e.g., turn down the volume; interpret pain as cold). Suggested displacement changes the location of the pain. Dissociation is used to separate pain from the patient's consciousness. Posthypnotic suggestion and self hypnosis are additional techniques used to expand pain relief.1

Parable

Parables involve the patient developing mental images associated with feelings of peace and calm. The patient is involved in decisions about image selection. Inclusion and emphasis on multiple senses enhance image clarity and facilitate the imaging process and
relaxation. When the patient is relaxed, he or she may be instructed to focus on images that represent pain. Patients are taught to modify images in a therapeutic manner. By doing so, he can experience a greater sense of control over pain.¹

**Superior hypogastric plexus block**

This procedure is indicated for pelvic pain that is not responsive to lumbar or caudal epidural block. The hypogastric plexus contains visceral sensory fibers which pass through the lower spinal cord. These blocks are usually suitable for patients with cancer of the cervix, uterus, bladder, prostate, or rectum, and may also be effective for some women with chronic noncancerous pelvic pain.¹⁰

The hypogastric plexus contains not only postganglionic fibers derived from the lumbar sympathetic chain, but also visceral sensory fibers from the cervix, uterus, bladder, prostate and rectum. The superior hypogastric plexus is usually located just to the left of the midline in the L5 vertebral body and below the aortic bifurcation. The fibers of this plexus divide into left and right branches and descend to the pelvic organs via the left and right inferior hypogastric and pelvic plexuses. The inferior hypogastric plexus also receives preganglionic parasymp fibers from the spinal nerve roots S2-S4.¹⁰

This is performed by placing the patient in a prone position, and a 15 cm needle is inserted approximately 7 cm lateral to L4-L5 between the vertebrae. The needle is directed medially and caudally under fluoroscopic guidance or ultrasound so that it passes through the L5 transverse process. In its final position, the needle should be anterior to the intervertebral disc between L5 and S1 and within 1 cm of the vertebral body in the antero posterior view. When fluoroscopy is used, radiopaque contrast injection confirms the correct position of the needle in the retroperitoneal space; 8 to 10 mL of local anesthetic is then injected. Superior hypogastric plexus block can also be performed using a transdiscal approach, although there are disc risks associated with this procedure. Complications including intravascular injection and bowel and bladder dysfunction may occur.¹⁰

**Acupuncture**

Acupuncture can be a useful adjunct management for patients with chronic pain, particularly those associated with chronic musculoskeletal disorders and headaches. This technique involves inserting needles into anatomically defined points, or so-called meridians. Needle stimulation after twirling insertion or application of a light electric current. The insertion point appears to be unrelated to the conventional anatomy of the nervous system. Although the scientific literature on the mechanism of action and role of acupuncture in pain management is controversial, several studies have shown that acupuncture stimulates the release of endogenous opioids, as opposed to its effects by naloxone.¹⁰
Figure 1. Pathway of pain
Quoted from Morgan\textsuperscript{10}

Figure 2. Lateral (A) and coronal (B) views of the brain showing the location of the primary sensory cortex.
Quoted from Morgan\textsuperscript{10}
Figure 3. Rexed spinal cord lamina.
Quoted from Morgan\textsuperscript{10}

Figure 4. Mechanisms of cancer pain as a direct consequence of tumor
Quoted from Hanna\textsuperscript{6}
Figure 5. Mechanism of bone pain in cancer patients
Quoted from Hanna

Figure 6. Mechanisms of neuropathic pain
Quoted from Hanna
Figure 7. Mechanism of pain in cancer patients as direct consequence of anticancer treatment
Quoted from Hanna⁶

Figure 8. A stepwise approach to pain management
Quoted from Blodendell²⁰
Table 1. Conversion of preferred opioid agents as recommended by the national comprehensive cancer center guidelines

| Agent       | Parenteral dose (mg) | Oral dose (mg) | Factor (IV PO) | Duration of action (hours) |
|-------------|----------------------|----------------|----------------|--------------------------|
| Morphine    | 10                   | 30             | 3              | 3-4                      |
| Hydromorphone | 1.5                 | 7.5            | 5              | 2-3                      |
| Levorphanol | 2                    | 4              | 2              | 3-6                      |
| Oxymorphone | 1                    | 10             | 10             | 3-6                      |

Quoted from Hanna\(^6\)

Table 2. Comparison of some commonly prescribed opioid analgesics.

| Agent          | Administration route | Relative effective vs morphine PO | Maximum daily dose | Initial dosage |
|----------------|----------------------|-----------------------------------|--------------------|----------------|
| Opioids are weak | PO                   | 0.17                              | 240 mg             | 60 - 120 mg    |
| Dihydrocodeine  | PO                   | 0.1 - 0.2                         | 400 mg             | 50 - 100 mg    |
| Tramadol        | PO                   | 0.1 - 0.2                         | 400 mg             | 50 - 100 mg    |
| Strong opioids  |                      |                                   |                    |                |
| Morphine        | PO                   | 1                                 | No limits          | 20 - 40 mg     |
| Morphine        | IV                   | 3                                 | No limits          | 5 - 10 mg      |
| Hydromorphone   | PO                   | 1.5 - 2                           | No limits          | 20 mg          |
| Oxydodone       | PO                   | 7.5                               | No limits          | 8 mg           |
| Fentanyl        | Transdermal          | +4                                | No limits          | 12 ug/ jam     |
| Buprenorphine   | PO                   | 75                                | 4 mg               | 0.4 mg         |
| Buprenorphine   | IV                   | 100                               | 3 mg               | 0.3 - 0.6 mg   |
| Buprenorphine   | Transdermal          | +4                                | No limits          | 10 mg          |
| Methadone       | PO                   | 4/ 8/ 12                          | No limits          | 10 mg          |

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