Chapter 2
Cancer Pain

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Introduction

Cancer pain is a subjective sensation of tissue damage, which has an adverse influence on multiple domains in an individual's life. Severe pain is associated with decreased function, increased interference with daily activities, depression, and anxiety. Pain is a major problem in 25–30% of individuals with newly diagnosed cancer and 70–80% with advanced cancer. Over 500,000 Americans die of cancer each year corresponding to 1,500 deaths per day [1]; therefore, cancer pain is a major problem that cancer specialists face. The lifetime probability of invasive cancer is 45% for men and 38% for women. Among men, prostate, lung, colon, and rectal cancers account for 50% of newly diagnosed cancers. Breast, lung, and colorectal cancers account for 50% of cancers in women. [1] As a result, bone and visceral pain are major pain subtypes clinicians need to manage.

Over 20% of individuals who have cancer pain also have pains related to treatment [2]. Over 60% with chronic pain have breakthrough pain. Most chronic pain is moderate to severe (>7 on a numerical rating scale where 0=no pain, 10=severe pain). Many suffer pain for months. There are 22 commonly classified cancer pain syndromes. These syndromes involve bone and/or joint lesions in 41%, visceral metastases in 28%, soft tissue in 28%, and pain from peripheral nerve injury in 28% [2]. Individuals frequently experience two or more distinct cancer pain syndromes. Nociceptive pain accounts for 72%, visceral pain 35%, and neuropathic pain (mixed or purely neuropathic) is experienced by 48% of individuals [2]. Factors associated with the greatest chronic pain intensity are the presence of breakthrough pain, bone, and neuropathic pain. Individuals less than 60 years and those with poor performance score will experience severe pain more frequently [2].

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Pain and Nociception

Rene Descartes in the 1600s articulated the theory that pain is conveyed by special nerves to the brain [3]. Nerves carry information about tissue damage to the central nervous system (CNS). This is termed nociception, which involves transduction of the electrical signals to the dorsal horn of the spinal cord, transmission through the superficial layers of the dorsal horn, through the contralateral spinothalamic tract or the ipsilateral dorsal column (in case of visceral pain) to the cerebral pain matrix. Nociception is modulated or gated through the spinal cord, brainstem, and supraspinal sites. Individual genetic makeup, prior experiences, physiological status, appraisal of the meaning of pain, mood, and social cultural environment modulate the conversion of nociception to pain [4]. Nociceptive stimuli are capable of eliciting pain but are not equated with pain. Pain is defined as "sensory and emotional experience associated with actual or potential tissue damage" and not tissue damage per se. There is a poor correlation between the degree of tissue damage and pain severity [4]. Acute pain is of short duration and is associated with a high level of physical pathology. Chronic pain (by definition >3–6 months) has low physical pathology because chronic pain tends to be perpetuated by factors that are both pathogenetically and physically remote for the original cause [4]. The degree of tissue injury does not correlate well with the pain severity for two reasons: (1) persistent pain alters the CNS, resulting in facilitatory pain transmission and modulation (neuroplasticity) [5, 6]; (2) affective and cognitive factors associated with unrelieved pain interact with tissue damage and contribute to persistent pain and illness behaviors [4]. Prolonged uncontrolled pain kills [7]. It is therefore important that clinicians manage cancer pain aggressively.

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The Anatomy of Pain

Vanilloid, Sodium Channels, Acid-Sensing Channels

Both A-delta (lightly myelinated) and C nerve fibers (unmyelinated) are "pain fibers," which slowly conduct impulses; they have high thresholds and are often "silent" except with noxious stimuli (Fig. 2.1). Transient receptor potential vanilloid receptor-1 (TRPV-1) respond to heat and capsaicin (found in peppers) (Fig. 2.1) [8]. TPRV-1 receptors are activated by various kinases (protein kinase A, protein kinase C, phosphatidylinositol-3-kinase). These kinases are, in turn, activated by inflammation [9]. Certain sodium channels are also activated or modulated by nerve injury (Na1.3, Na 1.8, Na 1.9), which facilitates nociception. Neuropathic injury increases certain sodium channel expression, channel trafficking in axons, and channel phosphorylation. As a result, surviving sensory nerves develop increasing responsiveness. Certain adjuvants (lidocaine, bupivicaine, tricylic antidepressants, topiramate, lamotrigine, and carbamazepine) block sodium channels and reduce neuropathic pain [10, 11]. Metastases are frequently hypoxic in the center, resulting in an acidic environment. Osteoclasts stimulated by metastatic cells within the bone trabeculae require an acidic environment (pH 4–5) for osteolysis. Both stimulate acid-sensing ion channels (ASIC), which increase sensory afferent depolarization [12].

Bone Pain

Bone pain has a unique spinal cord "signature," which is a combination of neuropathic and inflammatory pain. Continuous pain in addition to activation of ASIC involves local production of prostaglandin and endothelin, which stimulates pre- and postsynaptic afferent nociceptors in marrow spaces. As tumor grows within marrow, it destroys medullary sensory afferents. TPRV-1 receptors are also activated. Bone destruction leads to mechanical instability and periosteum nerve impingement. In the dorsal horn, sensory neurons produce and express C-fos, and astrocytes around secondary sensory neurons are activated and multiple in numbers [12–14]. For this reason, nonsteroidal anti-inflammatory drugs (NSAIDS) and gabapentin (an anticonvulsant commonly used for neuropathic pain) reduce bone pain [15].

Other Allergic Medications

Neurokinins such as substance P are released by peripheral and central sensory neurons and bind to NK-1 receptors. Substance P causes neurogenic inflammation, hyperalgesia, vascular changes (increased permeability and dilatation), and increases prostaglandin production. Bradykinin and certain cytokines (interleukin-1 and tumor necrosis factor alpha) induce hyperalgesia through production of

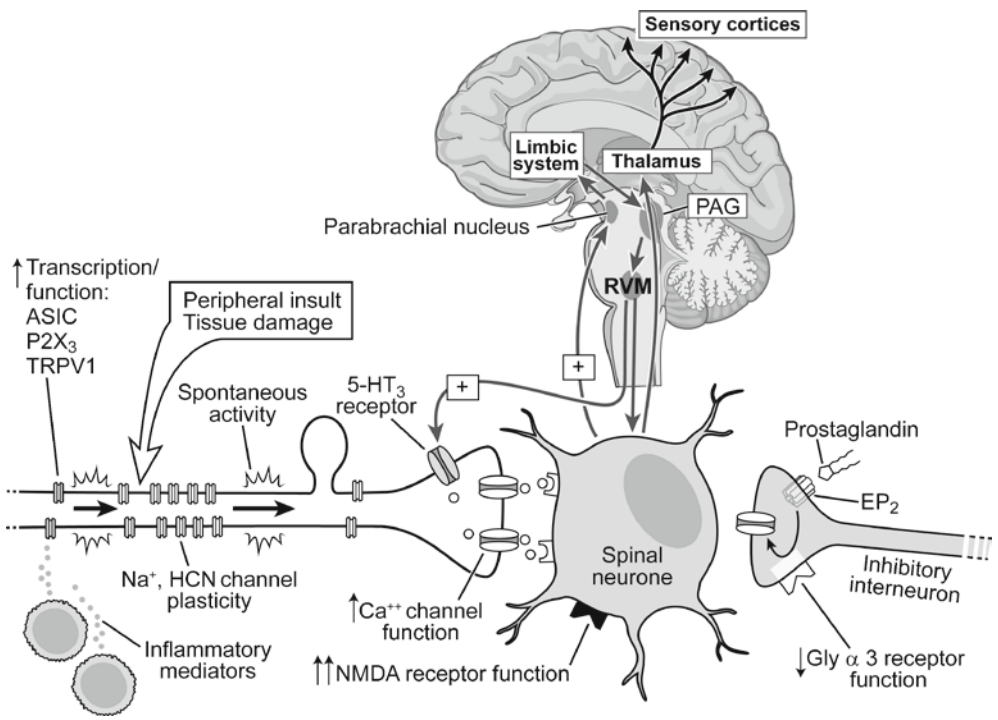

Fig. 2.1 Anatomy of pain

prostaglandins [16]. Nerve growth factors maintain and stimulate sensory nerve regeneration and are avidly taken up by membrane receptors. It also stimulates production of substance P [16].

Calcium Channels, NMDA Receptors

Several types of calcium channels are present in sensory afferents, which facilitate conduction, transmission, and modulation of pain. N-type calcium channels contain alpha$_2$ delta subunits that are targeted by gabapentinoids. *N*-methyl-D-asparate (NMDA) receptors require glutamate (released presynaptically) and glycine to be activated. Activation results in removal of magnesium from the center of the channel, which then allows calcium to enter. NMDA receptors are largely responsible for maintaining pain through "wind up" from repetitive stimulation of wide dynamic range neurons by primary afferents [16]. Increasing intracellular calcium leads to depolarization. NMDA receptors are noncompetitively blocked by ketamine.

A common pathway to pain is by way of prostaglandin (PGE_2) production. PGE_2 binds to multiple receptors (EP_1–EP_4) to activate neurons. PGE_2 alone does not produce pain but is necessary for induction of pain by other mediators, such as histamine and bradykinin. PGE_2 amplifies pain. Prostaglandins are not stored (which differs from other mediators of pain) but are synthesized at the time of depolarization by membrane-bound prostaglandin synthase and cyclooxygenase [17]. Prostaglandin synthesis uses arachidonic acid mobilized from membranes. PGE_2 is released and binds to multiple EP receptors both pre- and postsynaptic. Cyclooxygenase 1 and 2 are the important enzymes in PGE_2 production and are amplified peripherally and centrally within neurons and glia with inflammatory and neuropathic pain. Both NK-1 receptors and NMDA receptors increase cyclooxygenase transcription in the spinal cord [17]. Central nervous system cyclooxygenase is much more responsive than peripheral mechanisms to NSAIDS [17]. NSAID levels are measurable in the CNS within 15–30 min of administration. Certain NSAIDS (ibuprofen, indomethacin, and ketoprofen) have CNS levels that exceed plasma levels [17]. CNS nociceptive transmission inhibition is one of the more important components to NSAID analgesia [18]. Cyclooxygenase 2 is not the only enzyme to be targeted by NSAIDS. Cyclooxygenase 1 in the brainstem (periaqueductal gray) controls A-delta and C fiber-evoked spinal nociception. Cyclooxygenase 1 blockade within the periaqueductal gray (PAG) is important to analgesia [19]. Hence, broad, nonselective NSAIDs should be used to treat cancer pain as there are no trials of cyclooxygenase 2 selective inhibitors in cancer pain.

Central Excitatory Mechanism

Primary sensory afferents synapse on superficial laminae of the dorsal horn (lamina I and II). Secondary afferents cross over to the contralateral lateral funiculus and ascend as the spinothalamic tract. The spinothalamic tract projects to the brainstem, PAG, rostral ventromedial medullary (RVM), thalamus, nucleus tractus solitarius, and medullary reticular formation. These fibers contain substance P and NK-1 receptors [8]. In the deeper laminae of the dorsal horn reside wide dynamic range neurons that respond to a wide variety of painful stimuli. These secondary neurons are activated by repetitive release of substance P and glutamate from primary afferents. These neurons produce a prolonged amplified signal (wind-up) and increase synaptic transmission efficiency [8, 20]. Wide dynamic range neurons are blocked by inhibitory interneurons and monoamines (mainly norepinephrine) [9]. Wide dynamic range neurons also project to the thalamus by way of the spinothalamic tract.

The gate control theory proposed by Melzack and Wall in 1965 involved a descending modulatory/facilitatory system that gated nociceptive transmission through the dorsal horn [21]. The descending limb of the spinobulbospinal loop arises from the PAG, and RVM modulate spinal cord neurotransmission. The locus coeruleus, which contains norepinephrine, is also involved in modulation along with the PAG and RVM. The descending limb facilitates or inhibits nociceptive traffic at the level of dorsal horn, and descends through the dorsal funiculus [9]. Descending facilitation leads to central hypersensitivity (allodynia) and hyperalgesia. This facilitation is mediated by a particular serotonin receptor ($5HT_3$). This receptor is blocked by ondansetron. This may explain why selective serotonin reuptake inhibitors (SSRI's) are less effective than tricyclic antidepressants (TCAs) and selective norepinephrine serotonin reuptake inhibitors (SNRIs) in treating central sensitization and neuropathic pain [9]. Paradoxically, $5HT_3$ receptors are needed for gabapentin to work optimally as an analgesic [5].

Cerebral Pain Matrix

The cerebral cortex "pain matrix" consists of a cerebral cortex medial and lateral pain matrix system. The medial system (prefrontal cortex, insular cortex, cingulate gyrus, and amygdala) is involved in the affective and motivational response to pain. The lateral sensory cortex locates the site of pain. The medial system receives projections from the medial thalamus as well as ascending projections from the brain stem. The sensory cortex receives input from the ventrioposteriolateral thalamus. The spinothalamic tract

projections are devoid of motor neuron projections, which can be interrupted by anterolateral cordotomy without producing motor deficits [16].

Visceral Pain

Visceral sensory afferents travel with abdominal sympathetic afferents arising from internal organs and converge on the celiac plexus within the abdomen or thoracic paravertebral sympathetics in the chest. In the pelvis, the sensory afferents ascend with parasympathetics. Visceral afferents converge with somatic sensory afferent neurons on the dorsal horn. For this reason, somatic referral pain frequently occurs with severe visceral pain. Pain from pancreatic cancer, as an example, is referred to the abdomen, back, or shoulder. Lung cancer will refer pain to the ear, mediastinum, or back [16]. Visceral afferents terminate in lamina I, IV, and ventral horn. Secondary visceral sensory afferents ascend in the dorsal column of the spinal cord rather than the lateral funiculus. Celiac, hypogastric, or splanchnic blocks effectively reduce visceral pain, as does medial myelotomy at the level of the cervical cord (where the dorsal column projections cross over to the contralateral side) [16].

Opioid Receptors

In 1973, morphine was found to bind to particular sites within the brain called "morphine receptors" [22, 23]. Two years later, endogenous opiate peptides were discovered. Three major receptors have been described and are located on peripheral afferents, within the dorsal horn, visceral afferents, within the brain stem, and cerebral pain matrix [22]. Mu receptors are divided into high affinity (mu_1) and low affinity (mu_2) receptors. Mu_2 receptors produce respiratory depression, pruritus, prolactin release, physical dependence, anorexia, and sedation, whereas mu_1 receptors produce analgesia, euphoria, and serenity. Kappa receptors produce analgesia sedation, dyspnea, dysphoria, and respiratory depression. Both mu and kappa produce constipation by binding to receptors on enteral neurons [23]. The actions of delta receptors are not well known but are upregulated when mu receptors are activated and may facilitate pain control. Separate genes are responsible for each of the major opioid receptors; receptor subtypes are produced by mRNA splicing. Opioid receptors are found on pre- and postsynaptic A-delta and C fibers [22]. Activation results in inhibition of calcium channels, reduction in adenyl cyclase, and stimulation of inward rectifying potassium channels [23]. These three mechanisms prevent neuron depolarization and release of substance P and glutamate. Opioids inhibit gamma aminobutyric acid release by interneurons and increase dopaminergic neurotramission and prolactin release. Opioids reduce gonadotropin release from the hypothalamus. This leads to reduced libido and impotence. The rewarding effects of opioids. Are due to release of dopamine in the nucleus accumbens.

There are three majors types of opioids used to treat cancer pain: phenanthrenes (represented by morphine), phenylpiperidines (represented by fentanyl), and diphenyl heptanes (represented by methadone). Tramadol resembles venlafaxine; however, the metabolite, 0-desmethyl tramadol, is a mu agonist. Each opioid binds to receptors with different affinity, producing a different conformation, resulting in a different set of G protein interactions. Some opioids internalize receptors. Morphine causes receptor inactivation without internalization [24]. Opioid receptor affinity and opioid receptor activation are two different properties of opioid ligands. A ligand may poorly activate the receptor (low intrinsic efficacy) but have a high affinity for the receptor [22]. Differences in opioid responses between individuals are determined mainly by differences in opioid receptor pharmacodynamics rather than individual differences in opioid metabolism and clearance (pharmacokinetics) [25]. Low intrinsic efficacy opioids require more opioid receptors to be bound for the same degree of analgesia relative to high intrinsic efficacy opioids. As a result, a "ceiling effect" to analgesia occurs with low intrinsic efficacy opioids at high doses or high pain intensities, which alter equianalgesic ratios. This is one reason why morphine–methadone equivalents change with morphine doses [22]. Opioids have a log linear response with dose; doses are generally limited by side effects, not analgesia [22].

Opioid Tolerance

Chronic opioid exposure leads to an "antiopioid" response, which lasts longer than analgesia. This antiopioid response causes a withdrawal syndrome when opioids are suddenly stopped. Opioid receptors activate various kinases, which in turn phosphorylate NMDA receptors rendering them active. Opioid receptor phosphorylation leads to receptor inactivation and internalization [24]. Go/i proteins switch to G_z proteins with analgesic tolerance causing activation of neurons. Receptor activation is curtailed through phosphorylation of certain regulatory proteins (RGS) [24, 26]. A change in opioids (opioid rotation) may reverse opioid tolerance and enhance pain control. In rare cases, opioid ligands facilitate pain that becomes neuropathic in character. Opioid dose titration will cause increasing pain. Dose reduction in this situation paradoxically reduces pain. The use of certain adjuvant drugs such as ketamine blocks opioid tolerance and facilitates pain control [5, 16, 26, 27].

Cancer Pain Assessment

Pain is a multidimensional experience though most experts believe pain intensity is most important [28] (Table 2.1). Multidimensional pain questionnaires most frequently measure pain intensity, location, and relief; temporal pattern is often not included [28]. Paradoxically, temporal pattern is most important to opioid dosing strategies [29, 30]. Worst pain and average pain severity over 24 h correlates with interference with daily activities. Breakthrough pain episodes are also critical to assessment. Numerical rating scales (0 = no pain, 10 = severe pain) are preferred to 10 cm. visual analog scales. Verbal rating scales or even observations for pain behaviors are helpful in assessing the cognitively impaired and in those suffering from dementia [31].

Pain qualities are reported to be helpful in determining pain mechanisms. "Numbness," "pins and needles," and "burning" pain occurring within an area of sensory or motor deficit is usually neuropathic pain. Bone pain has an ache-like quality and is worsened with movement. Hyperalgesia (increased sensitivity to touch) occurs with inflammatory, bone, or neuropathic pain [31]. Pain qualities contribute to pain interference independent of severity. Deep pain, sharp pain, sensitive, or itchiness qualities interfere with daily activity [32].

Multidimensional scales provide a more comprehensive pain assessment. However, certain tools such as the Brief Pain Inventory may not be sensitive to changes in pain over time. Unidimensional pain intensity scales are validated and sensitive to changes in pain [33]. Pain interference may improve before severity. Pain relief may be experienced while pain intensity is still moderate or severe [31]. Asking "do you think your analgesics need to be increased (or decreased)" allows patients to find their personal acceptable relief as they judge benefits and risks of opioids. Recall fades with time; pain diaries, which include intensity and opioid doses, recorded several times during the day are helpful between clinic visits [31] (Table 2.2).

Table 2.1 Dimension of pain

Intensity
Affect
Interference
Temporal Pattern
Location
Referral
Quality
Duration
Beliefs (attitude/coping)
Pain history (diffuse noxious inhibitory control)
Treatment (worsening/relieving factors)

Table 2.2 Five axes for classifying pain into syndromes

I.	Anatomical Region
II.	Organ system that is producing pain
III.	Temporal characteristics
IV.	Pain intensity and pain onset
V.	Proposed pain etiology

Source: Data from refs. [28, 31, 33]

In those with cancer and reduced cognition a questionnaire with 13 or more items in a multidimensional scale will have a significant number of items left blank by individuals [34]. The Brief Pain Inventory is completed by <60%, whereas a 9–10 item scale has a completion rate of 84% [35]. Verbal scales are better for those on palliative wards, but this reduces the possibility of detecting small but perhaps important differences in pain with treatment [34]. Individuals with a Mini Mental State Examination Score of <24 (0–30) have poor completion rates for multidimensional questionnaires [34].

Pain trials use the sum of pain intensity differences over time (SPID), total pain relief (TOTPAR), side effects, and patient global medication performance (satisfaction, preference) as outcomes [36]. Pain intensity differences of 33% are clinically meaningful [36, 37]. Two types of methods have been used to test analgesics. An anchor method uses the percentage of responders (the number with a 33–50% reduction in pain intensity or 2 point decrease in an 11-point numerical scale) and compares responders in terms of numbers needed to treat NNT. The numbers needed to treat and numbers need to harm (NNH) gauge analgesic efficacy [38]. The second method uses changes in mean intensity of the entire group. These trials can be powered to show differences in group mean intensity scores yet have little clinical relevance. Changes in mean intensity scores can reflect a large response in a few individuals or a small, perhaps clinically insignificant response, in a large number of individuals [38].

Imaging Pain

Skeletal Metastases

Plain radiographs of painful bone sites are recommended for screening purposes. Over 50% of bone cortex has to be destroyed before lesions are visualized by plain radiographs [3]. Bone fracture is unlikely if <50% of the cortex is lost, whereas fracture should be anticipated if >75% of the cortex is lost. Surgeons use plain radiographs to determine the need for surgical intervention for this reason. Bone radiographs are preferred in myeloma over bone scans since

osteolytic lesions are poorly visualized on bone scans [39]. One of the first signs of vertebral metastases visualized by plain radiographs is the "winking" owl sign due to the loss of a pedicle arising from tumor extension from the posterior vertebral body [40].

Skeletal metastases almost exclusively arise from hematogenous spread to red marrow. Bone is more frequently a site of metastases than anticipated based on percent of cardiac output and blood supply [3]. The distribution based on bone scans are: 39% vertebral, 38% ribs and sternum, 12% pelvis, and 10% long bones [3]. Pain is experienced in only a minority of bone metastases. Painful symptomatic vertebral metastases and spinal cord compression occur more often with thoracic spine metastases (70%) than lumbar (20%) or cervical spine (10%) [40]. Bone scan positivity is due to reactive osteoblastic activity around metastases, which does not occur with osteolytic metastases. Nearly 25% of positive bone scan uptake is related to nonmalignant causes. Bone scans have a high sensitivity, but low specificity and should not be interpreted without clinically relevant data. Metastases, if present diffusely in the red marrow, will cause the red marrow to expand, resulting in diffuse juxtarticular uptake and absence of the kidney shadows (super scan). This may be mistaken for a normal bone scan [3]. Bone scans will worsen as patients respond to treatment (flare). Osteolytic lesions regress, and osteoblasts fill in with healing bone.

Computer tomography scanning (CT scans) is cumbersome when imaging bone and has limited views of the bone structures relative to magnetic resonance imaging (MRI). However, CT scans are more sensitive in detecting bone metastases than plan radiographs and can clarify bone scan positive painful and suspicious lesions in individuals unable or intolerant of MRI scanning [39]. CT scans will detect marrow metastases before bone destruction by differences of >20 Hounsfield units relative to normal fat containing marrow [39].

MRI skeletal metastases have low signals on T_1 weighted images (marrow has high intensity). Fat suppression T_1 images separate local fatty deposits from metastases. T_2 weighted images demonstrate enhancement relative to marrow signals. This is due to the high water content of metastases. A rim of bright T_2 enhancement can occur around metastases (halo sign) [39]. MRI is particularly suitable for vertebral lesions and, in addition, will image epidural metastases and spinal cord compression. Gadolinium-enhanced images better define epidural spaces and spinal soft tissues but are not needed for imaging bone. T_1 sequences can be used to differentiate benign from malignant vertebral fractures [40]. Malignant rather than benign vertebral compression fractures are evidenced by pedicle, posterior vertebral element involvement, or the presence of epidural or paravertebral masses. MRI is also able to image marrow and has been used to stage malignancies such as multiple myeloma for this reason [39].

Liver and Abdominal Imaging

Liver imaging has size limitations when used to screen for cancer. Metastases less than 1 cm are difficult to visualize or classify. For each metastatic lesion found, one to four cannot or will not be visualized due to size [41]. Edge definition is most important for visualizing liver metastases. Cysts have greater edge definition than metastases and hence are better visualized.

Liver ultrasounds are relatively inexpensive, do not involve radiation, and are portable but are operator-dependent [41]. Ultrasound images are limited by the acoustic window. Intervening gas and obesity limit image capability. High-frequency transducers increase lesion detection. Doppler ultrasounds may detect liver metastases by edge definition and by increased hepatic artery blood flow to metastases.

Iodine contrast is needed for liver CT scans to provide optimal imaging. Manipulation of arterial and portal contrast phase sequences help define metastases. Early enhancement during the arterial phase is common with breast and renal cancer, melanoma, and sarcoma [41]. Hypovascular tumors are better seen in the portal phase. CT portography bypasses the hepatic artery; the liver will be enhanced, while cancer remains unenhanced [41].

T_2 weighted enhancement on an MRI is characteristic of liver metastases. Contrast or dynamic scans using gadolinium are generally not helpful. However, certain agents (Mn-DPDP, Gd-BGPTA) are selectively taken up by hepatocytes or reticuloendothelial cells and will give a better edge definition to liver metastases [41].

Lung Imaging

Contrast enhanced CT scans of the lung should extend to the level of adrenals and liver in order to detect metastases [42]. CT scans better define metastases seen on screening chest radiographs and will detect lesions not seen by a standard anterioposterior chest x-ray. However, lesions less than 1 cm are difficult to define. CT scans have 61% sensitivity and 79% specificity for mediastinal involvement [43]. Positron emission tomography (PET) scanning combined with chest CT scanning better define lung lesions as malignant or benign and mediastinal node involvement. Whole-body PET scanning will detect distant metastases. Because the brain avidly takes up glucose,

either a CT scan or MRI of the brain will be needed to detect brain metastases [44].

Cancer Pain Management

The World Health Organization defined three levels of treatment based on pain severity: for mild pain, a nonopioid analgesic (NSAID or acetaminophen) plus an adjuvant; for moderate pain, a weak opioid (tramadol, codeine) plus adjuvant; and for severe pain, a potent opioid plus adjuvant [45–48]. An adjuvant analgesic is, by definition, a drug whose primary indication is for another reason but is analgesic in certain painful conditions. Tricyclic antidepressants, duloxetine, venlafaxine, and gabapentin are adjuvant analgesics.

There are five essential principles to chronic pain management: (1) oral administration is preferred; (2) drugs should be given proactively around the clock to prevent pain from recurring rather than on an "as needed" basis; (3) drug administration should conform to the 3-step analgesic ladder; (4) administration must be individualized due to wide interindividual variability in opioid requirements; and (5) attention to details is needed in order to sculpt opioid administration to temporal pain pattern and repeat assessment at intervals consistent with opioid half-life and pain characteristics (acute or chronic) should follow the dosing strategy [48]. The treatment strategy should be explained and written down for the patient. Most will experience breakthrough pain and not infrequently experience-opioid side effects. Most individuals will require an around-the-clock opioid plus an immediate release potent opioid for breakthrough pain [30]. The use of two sustained release opioids for chronic pain or two immediate release opioids for breakthrough pain should be avoided [48]. Most individuals with cancer pain require less than 200 mg of oral morphine (or morphine equivalents) per day [49]. The majority of individuals (80%) will experience relief from cancer pain by using the 3-step analgesic ladder and five basic principles [46].

Morphine remains the opioid of choice since no potent opioid is a better analgesic than morphine. Morphine is readily available in many countries, versatile as to its route of administration, relatively inexpensive, and has the greatest published experience [46, 50]. There is no difference in pain relief using sustained release morphine at 12- or 24-h intervals compared to immediate release morphine at 4-h intervals. Initial doses are 15 mg every 12 h of sustained release or 5 mg every 4 h of immediate release morphine in the opioid naïve. Low doses of potent opioids can be substituted for "weak" opioids on step 2 of the analgesic ladder [30, 45, 46]. Doses should be titrated to pain relief. The 4 h morphine requirements can range from 5 to ≥250 mg [45]. In place of morphine, oxycodone 5 mg every 4 h, hydromorphone 1 mg every 4 h, or fentanyl 12 mcg/h transdermal patch replaced every 3 days may be used [30]. Fentanyl patches are best used when chronic pain is well controlled by intravenous or subcutaneous fentanyl. The conversion to a patch is 1 to 1 relative to transdermal fentanyl but with wide differences among individuals in absorption from the transdermal patch.

The around-the-clock dose should not be changed until steady state. Individuals on 4 h morphine should have doses adjusted daily if necessary (the same is true for oxycodone and hydromorphone) [51]. Individuals on sustained release morphine should not have around-the-clock doses adjusted sooner than 48 h – the same is true for transdermal fentanyl. Pain flares and unsatisfactory control should be managed by adjusting rescue doses in the interim.

Breakthough Pain

Breakthrough pain includes several clinically distinct pains. The term "breakthrough" is problematic linguistically since literal translations do not exist in all languages [52]. "Episodic" or "transient" pain may be a better universal term. Episodic pain may be "incident" – or movement-related, which is either voluntary or involuntary (with hiccup or colic). Episodes may be spontaneous or occur at the time when the next opioid dose is due (end of dose failure) [52]. Transient pain is usually rapid in onset and short in duration. The offset of pain (30 min) is the average time to analgesia with oral immediate-release opioids [52]. Hence, oral immediate-release opioids may not be effective for this reason. The standard approach to the management of incident and breakthrough (spontaneous) pain is to give 10–20% of the total daily oral morphine dose as a rescue dose [30, 46, 52]. This may be repeated during a 4 h time period [46]. End of dose failure is due to suboptimal around-the-clock opioid doses and should be managed by increasing the sustained release opioid dose (or immediate release 4 h doses) before considering a shortened interval between doses; 8 h for sustained release morphine, 60–48 h for transdermal fentanyl, 3 h for immediate release morphine [30]. Several opioid preparations are available for incident or breakthrough pain: oral transmucosal fentanyl citrate and fentanyl buccal tablets [52]. Sublingual methadone also has a rapid onset to pain relief and parenteral morphine or hydromorphone using 1/6 of the total daily dose converted to parenteral equivalents have also been effective [52]. Both transmucosal and transbuccal fentanyl will need to be titrated to relief independent of the chronic opioid dose.

Rescue doses should be added to the chronic opioid doses if the transient pain is spontaneous. This should be done at

steady state. If pain remains poorly relieved and the patient is not experiencing dose-limiting toxicity (myoclonus, cognitive failure, nausea and vomiting, hallucinations), the total opioid dose (chronic plus rescue doses) should be increased 30% and rescue doses adjusted [30].

Rescue doses for incident should not be added to chronic doses if the baseline pain is under control [30]. Doses for incident pain should be increased independent of the around-the-clock doses if incident pain is poorly relieved. Doses should be increased 100% if <50% response and 50% if >50% response [30]. Rescue doses should also be increased if pain is relieved but rapidly returns before the next rescue dose [30].

Pain Control with Opioid Side Effects

Mild nausea and sedation from opioids usually improves over several days. Doses usually do not need to be adjusted. However, tolerance does not develop to constipation. All who are started on potent opioids should be started on laxatives and stool softeners [30]. In those with pain control but excessive opioid side effects, the chronic opioid dose should be reduced 30% and the rescue dose maintained. Reducing the chronic opioid dose may lead to resurgence of pain, and the rescue dose will be needed to control pain [51].

Uncontrolled Pain with Opioid Side Effects

Opioid dose titration is limited by side effects (Table 2.3). Strategies for managing pain include opioid rotation, route conversion or the addition of an adjuvant analgesic followed by opioid dose reduction [30, 45, 47–49, 53, 54]. These strategies have not been compared: opioid rotation; route conversion; or the addition of an adjuvant with opioid dose reduction are largely based on clinical experience and circumstances. Route conversion, which may be from oral to parenteral opioids, alters the ratio of morphine to metabolites, and thus reduces side effects. However, most route conversions for poorly controlled pain are to spinal opioids. Parental route conversions are usually done for other reasons: where oral administration is impossible due to nausea, dysphagia, mucositis, or bowel obstruction; for poor drug absorption due to dysfunctional or ischemic bowel, short gut syndrome, or fistula; to reduce the number of tablets; as a means of gaining rapid control of acute pain [29, 48].

Table 2.3 Guidelines for opioid rotations

1. Calculate equianalgesic dose then
   - Reduce 50% if rotation is primarily for side effects in the elderly frail, those experiencing side effects on high opioid doses or in those with compromised organ function
   - Reduce 30% in those who are relatively healthy on low or standard opioid doses and normal organ function who are experiencing side effects
   - Use the equianalgesic dose if rotations is predominantly for pain
2. Adjust doses based on comedications, which interfere or alter with opioid clearance
3. Methadone equianalgesic doses should be reduced 75–90%, or a different dosing strategy should be used, which involves an every 3 h as needed dose using 10% of the total daily morphine equivalents. Alternatively a linear equivalent dose can be given every 8 h based on the following equianalgesic scale (morphine to methadone ratio)

4:1	<90 mg morphine/day
8:1	<300 and >90 mg morphine/day
12:1	>300 and <1,200 mg morphine/day
15:1	>1,200 and <2,000 mg morphine/day
20:1	>2,000 mg morphine/day

   Methadone should be prescribed by those with experience of using methadone
4. Provide a rescue dose preferably using the same opioid. The initial dose should be 10–20% of the total daily opioid dose
5. Do not adjust the chronic around the clock opioid dose until reaching steady state. Opioid rotation before reaching steady state is meaningless and dangerous
6. Frequently assess pain response and toxicity. Opioid toxicity may persist for several days. Rapid opioid rotations on a daily basis are dangerous. Methadone responses may not be seen for 1–2 days and steady state may not be reached for 3 days, so patients may experience pain for 1–2 days while rotating to methadone
7. Conservative equianalgesic ratios in one direction are not conservative when rotating back to the first opioid. There are bidirectional differences in opioid equivalents. Clinicians need to be aware that equivalents may not be "reversible" in direction
8. Add rescue doses to the around the clock dose then increase the total dose by 30–50% if baseline pain is uncontrolled at steady state
9. Add rescue doses (for nonincident pain) to the around the clock dose if pain is controlled at steady state and frequent rescue doses (>4) where needed in the last 24 h
10. Do not add adjuvants and rotate simultaneously. Do one at a time and assess analgesia before altering the strategy

Source: Data from refs. [30, 46, 51]

Table 2.4 Equianalgesia

Opioid	Oral	Parenteral
Morphine	30	10
Hydromorphone	6	2–3
Oxycodone	20–30	
Fentanyl	1:70	
Methadone	See Table 2.3	
Buprenorphine	Conversion similar to fentanyl	

Source: Data from refs. [49–51, 55, 56, 62]

Equianalgesia and Opioid Rotation

Opioid route conversion and opioid switch is needed in 40% of individuals with advanced cancer at some time during the course of their illness [55] (Table 2.4). Equianalgesia is the ratio of doses for two opioids, which result in the same degree of pain relief. This should be determined at steady state; however, most equianalgesic tables use single dose comparisons (nonsteady state) and summed pain intensity differences. The study design for equivalents is usually crossover or parallel with intraindividual (crossover) or interindividual (parallel) comparisons [56]. Most individuals in rotation studies are relatively opioid naïve and not highly opioid tolerant, which is not the usual case when rotations are done for cancer pain. Populations from whom equivalents are determined differ from populations in whom opioid rotations are performed. There are large variations in equivalents between individuals such that published equivalents have large confidence intervals but are reported as single ratios. Factors that significantly alter equivalents are age, polypharmacy, organ function, and opioid tolerance [56]. Opioid rotations utilize equianalgesia, but tables for the purpose of improving analgesia and/or reducing side effects [49, 57]. Almost all rotations involve a "Stop-Start" strategy where the first opioid is discontinued and the second is started. A "partial" opioid rotation where another opioid as an "added on" has little clinical evidence and is likely to lead to dosing error and/or reduced patient compliance.

Acute Pain

Severe acute or crescendo pain usually arises from complications related to cancer (bone fracture, perforated bowel). Strategies for managing pain are distinct from those used to treat chronic pain [29]. Morphine 1–2 mg every 1–2 min, fentanyl 20 mcg/min or hydromorphone 0.2 mg/min intravenously until pain control is an effective titration strategy [29]. This requires bedside titration by physicians with assessment of pain intensity every 1–2 min and a respite every 10 min. Alternatively, 1.5 mg of morphine can be given every 10 min or 10–20 mg every 15 min. The goal is significant but not complete pain relief with titration. The morphine dose which significantly reduces pain intensity, is then used as the 4 h dose by converting to oral morphine (parenteral dose multiply by 3) or continuous parental morphine by dividing the effective dose by 3 to 4 and using this dose as the hourly continuous dose. If individuals are on around-the-clock morphine, this will need to be added to the maintenance dose.

Patient-Controlled Analgesia

In the 1960s, analgesic responses to small intravenous doses of morphine by patient demand was found to be superior to intramuscular opioids given at a fixed dose as needed [58]. The experience with patient-controlled analgesia (PCA) taught us: (1) small increases in opioid serum levels can dramatically reduce pain; (2) there is a minimally effective analgesic concentration, which varied considerably among individuals; (3) there is no single effective analgesic serum concentration of morphine. Two prerequisites are needed for effective PCA: (1) individualized titration to pain relief and (2) maintenance of plasma opioid concentrations by demand only (opioid naïve) or continuous plus demand (in opioid tolerant individuals) dosing. For PCA to be successful, the demand dose should produce appreciable analgesia with a single activation [58]. Demand doses too low frustrate patients and demand doses too high (or activation frequency or intervals too short) lead to delayed opioid toxicity. A large number of PCA strategies have been published; in the opioid naïve, 1–4 mg at a 5–60 min lockout interval, and in the opioid tolerant, continuous morphine plus 1–20 mg of morphine at 20–60 min intervals. Some strategies use 25–50% of the hourly morphine dose as the demand, or 10% of the total daily morphine dose converted to parenteral equivalents as the demand dose [59]. In general, lockout intervals are longer if continuous morphine infusion is used.

Spinal Analgesia

Intrathecal and epidural opioid analgesia are effective in managing continuous deep somatic pain unresponsive to systemic opioids or in individuals experiencing dose limiting toxicity from systemic opioids [54]. Cutaneous pain and pain from intestinal obstruction are not responsive to spinal opioids. Sixty to 80% will experience relief. Adjuvant analgesics such as bupivicaine, clonidine, or the calcium channel blocker ziconotide are frequently needed to improve pain control. Spinal opioid rotation (morphine to hydromorphone or fentanyl) may improve pain that is not responsive to morphine [54]. Epidural opioids are used in those with only a

few weeks to survive, whereas intrathecal opioids are preferred in those expected to survive months. In general, 1% or less of the oral morphine dose is needed for effective spinal analgesia. Certain side effects related to the opioid (nausea, vomiting, sedation); pruritus, urinary retention, hypogonadotropic hypogonadism are more frequent with spinal opioids than systemic opioids. Clonidine and ziconotide may produce orthostatic hypotension. Major motor weakness can develop from a hematoma at the catheter insertion site or with high doses of bupivicaine [54].

Opioid Overdose

Respiratory depression occurs with opioid overdose. Tachypnea and dyspnea with sedation is usually not due to opioids. Overdose will reduce the respiratory rate and tidal volume leading to carbon dioxide retention. Opioid overdose is almost always accompanied by reduced consciousness and pupillary miosis. Dilated fixed pupils or unequal pupils are indications that the cause of reduced consciousness is the result of a stroke, hypoxia, or mass lesion rather than opioid. Individuals on stable doses of morphine for weeks may develop signs and symptoms of overdose from radiation induced pain response, progressive renal failure, drug interactions, or sepsis, which alters morphine or morphine 6-glucuronide clearance. To manage opioid overdose, dilute a 1 ml (0.4 mg) ampoule of naloxone to 10 mg of saline or glucose and give 1 ml intravenously every 2–3 min until the respiratory frequency increases to 10 per minute and sedation resolves. The goal is to reverse respiratory depression, not analgesia [38, 48]. The half-life of naloxone is 30 min, so repeat doses or continuous infusion may be necessary to reverse respiratory depression with methadone, transdermal fentanyl, or sustained release morphine.

Pain Management in the Actively Dying

Delirium occurs in 80% of those actively dying and so pain assessment will depend on non-verbal cues. Terminal restlessness is often related to delirium, fecal impaction, urinary retention, or poorly controlled pain. Opioid dosing should not be interrupted; rescue doses are used as a trial to see if restlessness improves, once sure that urinary retention or fecal impaction are not a problem.

Oral intake may be a problem such that an alternative route is frequently necessary. Conversion to rectal opioids (morphine, hydromorphone, oxycodone, and methadone) is 1 to 1. Sublingual morphine and oxycodone are poorly absorbed and have a delayed onset to action, so are not good choices. Sublingual methadone is relatively well absorbed and has a quicker onset to analgesia than oral morphine [52].

Adjuvant Analgesics

NSAIDs are technically analgesics rather than adjuvant medications. The addition of NSAIDs to morphine improves analgesia, and may reduce side effects by reducing morphine requirements by 30% [60, 61]. Adjuvant analgesics are added to improve pain control or to allow for opioid dose reduction in those with inadequately controlled pain and opioid side effects (Table 2.5). This strategy is effective and an alternative to opioid rotation and route switch. A listing of adjuvant analgesics is provided on Table 2.5.

Corticosteroids (dexamethasone 2–16 mg/day) reduce headaches from increased intracranial pressure, pain from soft tissue infiltration, nerve compression, or hepatomegaly [45]. Bisphosphonates (pamidronate 60–90 mg or zolendronate 4 mg monthly) relieve pain from bone metastases. Tricyclic antidepressants, gabapentin, pregabalin, duloxetine, and venlafaxine are equally effective in relieving neuropathic pain as determined by the NNT. However, the gabapentinoids are better tolerated and have fewer drug interactions. Two or three adjuvant analgesics may be needed for neuropathic pain [45]. Transdermal lidocaine is effective for mononeuropathies and postherpetic neuralgia. Transdermal lidocaine is not absorbed to any great extent, and is particularly safe in the elderly or for those on multiple psychotropic medications. Ketamine is a NMDA receptor antagonist, which is analgesic at subanesthetic doses [62]. Ketamine reverses morphine tolerance and can be used for breakthrough pain for those on systemic or spinal opioids. Oral doses are 25–50 mg three to four times daily or 0.1–0.5 mg/kg/h as a continuous infusion. Strontium-89 chloride and samarium-153 are absorbed in

Table 2.5 Adjuvant analgesic and nonopioid analgesics

Drug	Caution/side effects	Maximum dose/day
Acetaminophen	Hepatotoxicity	4,000 mg
Ibuprofen	GI, renal toxicity	3 × 800 mg
Naproxen	GI, renal toxicity	3 × 500 mg
Ketorolac	GI, renal toxicity	45 mg × 6 (sc/IV)
Etodolac	GI, renal toxicity	1,200 mg
Amitriptyline	Sedation, cardiac	50–225 mg
Nortriptyline	Sedation	50–225 mg
Gabapentin	Sedation	3,600 mg
Pregabalin	Sedation	600 mg
Carbamazepine	Sedation, myelosuppression	1,600 mg
Duloxetine	Headache, dizziness, sleepiness	120 mg
Venlafaxine	Headache, dizziness, sleepiness	225 mg

Source: Data from ref. [50]

areas of high bone turnover and will reduce pain from diffuse bone metastases over several weeks to months. Delayed myelosuppression limits repeated dosing. Baclofen reduces muscle spasm pain secondary to spinal cord compression, as does low doses of diazepam [63]. Methylphenidate improves opioid-induced somnolence as well as depression. Doses are 5–10 mg in the morning and at noon. Octreotide and anticholinergic medications reduce painful colic from malignant bowel obstruction [63].

Nondrug Treatment for Cancer Pain

Transcutaneous electrical nerve stimulation, acupuncture, single fracture radiation, and vertebral kyphoplasty can relieve poorly controlled pain [45, 53]. Hypnoses reduce procedural pain and mucositis. Cordotomy or rhizotomy, celiac or splanchnic blocks reduce morphine requirements and pain in those whose pain is not responding to opioids or who develop dose-limiting opioid toxicity [53].

Conclusion

Cancer pain is a composite of acute and chronic pain, which is tumor- or treatment-related in etiology. Individuals with cancer generally experience more than one pain during the course of their illness. Assessment is the key to effective management. The World Health Organization 3-step ladder and five principles form the foundation for medically managing cancer pain. Dosing strategies take into account pain intensity and temporal pattern to sculpt opioid doses to individual needs. Opioid rotation, route change, or the addition of adjuvant analgesics successfully relieves opioid poorly responsive pain.

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