Overview of Cancer-Related Pain
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Learning Objectives

By the end of this activity, participants should be able to:
1. Outline the pathogenesis of cancer pain.
2. Describe goals and challenges associated with analgesia in cancer patients.
3. Evaluate pain symptoms and infer pain etiology.
4. Recognize signs and symptoms of cancer pain syndromes.

Introduction

Cancer is characterized by abnormal cell proliferation and describes over 100 diseases. A common feature of these diseases is the propensity for pain. Cancer-related pain (CRP) is directly caused by cancer processes and healthcare interventions such as disease monitoring and treatment. Multiple painful stimuli and potentiating factors contribute to the complexity and challenges of treating CRP. Inadequately controlled pain may negatively affect sleep, cognition, emotional wellbeing, sexual function and cardiovascular health. Though evidence suggests that adequate pain control can be achieved for up to 90 percent of patients with guideline-based care, less success is achieved in practice.

Pharmacists are poised to significantly improve quality of life by implementing care plans and monitoring pain symptoms for patients with cancer. Opportunities to improve pain management are occur by active listening, accessibility and approachability. In direct care settings, pharmacists are essential for navigating pharmaceutical solutions to pain; particularly when it is severe, refractory or etiologically complex. Optimal care plans are evidenced-based and crafted with an understanding of patient preference, cancer pathology and pain expression.

Epidemiology

In 2014, over 14.7 million people in the United States had a cancer diagnosis, affecting approximately 4.6 percent of the population. The most commonly diagnosed cancers include female breast, prostate, lung/bronchus, colon/rectum and uterine. Pain prevalence varies throughout cancer treatment and is estimated at the following rates: 25 percent at diagnosis, 33 to 55 percent during treatment, 40 percent after curative treatment and 66 percent in advanced disease. About 2 to 10 percent of the pain reported by cancer patients is unrelated to cancer. The subjective nature of pain and variable methods of reporting are challenges for assessing management of cancer-related pain at the population level.

An observation of cancer pain syndromes (CPS) elucidates challenges of treating cancer pain. Over one-third of CPS patients have a pain intensity score of five or higher and two-thirds experience breakthrough pain. Moreover, one third of CPS patients suffer from more than one pain pathology. Cancer treatment is responsible for pain in approximately 20 percent of CPS patients and approximately 90 percent of CPS patients have tumor-associated pain. Bone and joints are the tissues most commonly involved with tumor-associated pain, followed by soft tissue, viscera and nervous tissue.

Pain Pathogenesis and Expression

Pain is caused by noxious stimuli that is chemical, physical or thermal in nature. A useful way to classify pain is by origin. Nociceptive pain describes the classical pain response occurring from
tissue injury, which is further differentiated as somatic or visceral. In contrast to nociceptive pain, neuropathic pain is associated with a stimulus within the nervous system and causes sensory abnormalities. Each pain type has distinguishable features which are clinically useful for stratification; however, it is important to recognize that this taxonomy is a simplification. For example, inflammatory pain may refer to a distinct type of pain, yet inflammatory processes are involved in both nociceptive and neuropathic pain. Similarly, psychogenic pain originates from psychological factors, yet all pain is subject to psychological influence.

The distinctive qualities of each pain type are used to infer pain etiology from descriptions of pain when physical evidence is not apparent. A summary of pain characteristics is listed in Table 1. Somatic nociceptive pain is characterized by aching, stabbing, throbbing, squeezing, tenderness and quality of depth. Examples of somatic nociceptive pain include bone metastases, wounds and mucositis. Relative to somatic nociceptive pain, visceral nociceptive pain may be more difficult to locate. Pain may be generalized or referred, meaning that it is felt in a part of the body other than the source. Qualities of visceral pain include sharpness, stabbing, squeezing, cramping and gnawing. Examples of pathology associated with visceral pain include organ metastases, bowel obstruction and urinary retention. In general, nociceptive pain is more responsive to conventional therapies than neuropathic pain. Hallmark descriptions of neuropathic pain include numbness, tingling, shooting and burning which may radiate along nervous tissue. Causes of neuropathic pain include spinal cord compression, phantom limb pain and peripheral neuropathy. Neuropathic pain may be associated with hyperalgesia or allodynia, conditions of increased pain sensitivity. In the case of allodynia, pain is provoked from stimuli that is normally innocuous.

Table 1. Pain Characteristics and Associated Pathology

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<tr>
<th>Pain Quality</th>
<th>Descriptions</th>
<th>Associated Pathology</th>
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<tbody>
<tr>
<td>Nociceptive</td>
<td>Somatic</td>
<td>aching, stabbing, throbbing, squeezing, tenderness, deep</td>
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<tr>
<td></td>
<td>Visceral</td>
<td>sharpness, stabbing, squeezing, cramping, gnawing</td>
</tr>
<tr>
<td>Neuropathic</td>
<td></td>
<td>numbness, tingling, shooting and burning</td>
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Pain generation and perception are not readily measurable. To make treatment decisions, clinicians rely on the subsequent step of the pain pathway: expression. Pain expression refers to signs of pain that are observable to people other than the patient. Pain expression is evident when patients recount his or her pain symptoms. Word choice, tone and nonverbal signs such as wincing are all components of pain expression. Importantly, pain expression is influenced by factors other than the patient’s perception of pain. These factors are termed pain modulators and include psychological distress, spiritual distress, chemical coping, mood disorders and cognitive impairment. Other factors include environment, culture and personality, which influence patient affect as well as the biases of the providers who care for them.
Cancer Pain Assessment

Pain assessments are an integral component of cancer pain management. The goals of assessment are to identify pain characteristics, pain etiology, specific pain syndromes and analgesic targets. New onset pain can be a sign of cancer progression. Therefore, all patients with active cancer should be screened at every encounter, and a positive pain screening indicates a thorough pain evaluation even if the patient is not seeking pain management.

The patient’s own report is the best way to determine pain quality and severity. Pain intensity is commonly quantified on a scale of one to 10 and described as either mild (one to three), moderate (four to six) or severe (seven to ten). Mnemonics aid the recall of important qualitative parameters including: site, onset, character, radiation, timing, exacerbating/relieving factors and severity (SOCRATES) and location, medical treatments, number of episodes, onset, position, quality, radiation, severity and triggers (LMNOPQRST). In addition, pain assessment tools facilitate communication between patient and provider such as body diagram mapping, qualitative surveys like the Pain Quality Assessment Scale (PQAS) and pictorial scales such as Wong-Baker FACES which was developed to help children communicate the intensity of their pain and features six faces expressing increasing discomfort. Pain assessment tools should be practical to use, easy for patients to understand and facilitate the trending of pain over time.

STOP AND REFLECT

Prior to her mastectomy, LL’s six of ten pain was well-controlled on a relatively stable opioid regimen. Six months later, LL reports persistent pain that bothers her multiple times per day despite taking a daily opioid regimen that is nearly double what she was taking prior to the surgery. What pain modifiers or changes in pain quality might be contributing to her poor pain control now? What clarifying questions could you ask?

Feedback
Psychological distress, hyperalgesia and/or mastectomy-associated neuropathic pain may contribute to her present status. Inquiring about psychiatric comorbidities, analgesic history and pain quality may clarify the presence of these factors.

Cancer Pain Assessment

STOP AND REFLECT

BR is a 57-year old accountant who presents with T3b prostate cancer and new onset pelvic pain. His native language is Spanish and he speaks English at the full professional proficiency level. Which tool is best for assessing his cancer pain?

A. FACES
B. Numeric scale 1-10
C. Body diagram mapping
D. Pain Quality Assessment Scale (PQAS)

Feedback
Answer B is the best option because it is simple to execute, quantifies pain intensity and facilitates tracking changes over time. Answer D includes qualitative questions in addition to a number scale. While PQAS generates more information than B, it is cumbersome and better-suited for neuropathic pain assessments and research applications. Answer C is not useful because his pain is localized. Like B, answer A measures pain intensity but with pictures instead of numbers. Because BR is an adult, there are no other indications in the case for using a pictorial scale.
Responsive care plans require an understanding of pain etiology, though the complexity of cancer pathology and treatment sequelae may make this difficult to ascertain. When pain etiology is obscure, clarifying information should be sought from additional sources. One strategy is to ask open-ended questions to patients, families and care providers about changes in clinical status or precipitating events. Other resources include the medical record and records from outside institutions such as care facilities or pharmacies. In some cases, laboratory work or imaging may be helpful for investigating suspected mechanisms. Importantly, involvement of a pain specialist should be considered for cases of refractory pain. Suboptimal cancer pain management is common, yet as many as 20 to 30 percent of oncologists rarely refer patients to a pain specialist.14

Cancer pain syndromes (CPSs) are constellations of pain and associated symptoms which are suggestive of underlying pathology. CPSs may be broadly classified as acute or chronic. Most acute cancer pain syndromes are adverse effects of treatment, whereas chronic pain syndromes are more often direct sequelae of cancer. Pathological mechanisms of cancer-induced CPSs include physical crowding, sensitization of nervous tissue and altered sympathetic drive. In addition to describing pain etiology, CPS identification may clarify clinical status, cancer progression and prognosis. For this reason, pain evaluations should aim to identify pain syndromes whenever possible. By the conclusion of the pain evaluation, analgesic goals must be discussed with the patient. At minimum, this conversation should address fears about pain and expectations of analgesia as they relate to function and comfort.

Principles of Cancer Pain Management

Cancer pain guidelines highlight the importance of interdisciplinary management, psychosocial support, patient education and nonpharmacological interventions in conjunction with pharmacotherapy for optimal pain management. The World Health Organization (WHO) guidelines are the most widely accepted resource on this topic.7 The WHO recommends a stepwise analgesic strategy that begins with non-opioid analgesics before initiating increasingly potent opioids. By contrast, the National Comprehensive Cancer Network (NCCN) guidelines reflect concern with undertreatment of cancer pain and provide stronger support for initiating treatment with an opioid.7 Both organizations provide guidance on pain assessment, drug selection, dosing regimens, monitoring and supportive care.

The WHO recommends non-opioids for initial treatment of cancer pain, including acetaminophen 650 to 1000 mg PO q4-6hr, aspirin 500 to 600 mg PO q4-6hr, ibuprofen 400 mg PO q4-6hr and indomethacin 25 mg PO q6hr. Opioids are recommended once pain is no longer controlled by non-opioids. Codeine is preferred by the WHO for mild to moderate pain, typically dosed 30 to 120 mg PO q4hr, while morphine is the preferred agent for moderate to severe pain. An initial IR morphine dose of 10 to 15 mg PO is appropriate for people who have received 60 to 100 mg of codeine and relief is usually achieved with 10 to 30 mg PO q4hr.15 Table 2 lists common opioid equivalencies. Importantly, recommendations by the WHO face limitations in practice. NSAID use may be contraindicated due to chemotherapy-induced thrombocytopenia and codeine use may be restricted due to interpatient variability in metabolism. As such, aspirin and codeine are rarely used in practice.

<table>
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<th>Table 2. Opioid Equivalencies7</th>
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<td>Parenteral Dose (mg)</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Morphine</td>
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<td>Hydromorphone</td>
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The National Comprehensive Cancer Network (NCCN) guidelines also propose non-opioids for initial management; however the recommendation is limited to mild pain. Preferred non-opioid regimens include acetaminophen 650 mg PO q4hr or 1g q6hr (max 4000 mg daily) and cautious use of NSAIDS. When possible, NSAID selection should begin with an agent that has been well-tolerated and efficacious in the past. Otherwise, ibuprofen 400 mg four times daily (max 3200mg daily), naproxen 220-500 mg two to three times daily (max 1500 mg daily) and ketorolac 15 to 30 mg IV q6hr (max five days) may be considered, among others. Short-acting opioids are the preferred initial agents for moderate to severe pain, dosed according to opioid tolerance. Tolerance is defined by the Food and Drug Administration (FDA) as 60 mg of oral morphine daily or an equianalgesic opioid requirement daily for a week.\(^7\) Initial dosing recommendations for opioid-naïve patients include short-acting morphine sulfate five to 15 mg PO, 2-5 mg IV or equianalgesic dose of another opioid. Opioid tolerant patients are initiated with 10 to 20 percent of the total opioid dose received within the previous 24hrs, excluding transmucosal fentanyl. Oral administration is most common, though other routes of administration should be considered to maximize patient comfort. Safety and efficacy is evaluated 60 minutes following oral administration and 15 minutes following IV administration.\(^7\) Table 3 summarizes analgesic recommendations by the WHO and NCCN for the initial treatment of cancer pain.

### Table 3. WHO and NCCN Recommendations for the Initial Treatment of Cancer Pain\(^7,15\)

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<thead>
<tr>
<th>WHO</th>
<th>NCCN</th>
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<td>Begin with a non-opioid. For pain that is uncontrolled with non-opioids, add a weak opioid for moderate pain or a more potent opioid for severe pain.</td>
<td>For mild pain, first consider a non-opioid. Short-acting opioids are preferred for moderate to severe pain.</td>
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<tr>
<td>- Codeine PO for mild to moderate pain, typically 30 to 120mg q4hr</td>
<td>For moderate to severe pain:</td>
</tr>
<tr>
<td>- Morphine PO for moderate to severe pain, typically 10 to 30 mg q4hr</td>
<td>- Opioid naïve: short-acting morphine sulfate five to 15 mg PO, 2-5 mg IV or equivalent</td>
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<tr>
<td></td>
<td>- Opioid tolerant: 10 to 20 percent of total opioid dose received over previous 24 hours, excluding transmucosal fentanyl</td>
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Once titrated to adequate relief and oral therapy is appropriate, patients may be transitioned to a maintenance regimen with a scheduled long-acting opioid to support adherence. This should be combined with a short-acting opioid for breakthrough pain. The WHO suggests dosing at 50 to 100 percent of the four-hour maintenance dose, which is equivalent to 8.3 percent to 16.6 percent of the daily regimen.\(^15\) Similarly, NCCN states that the typical rescue dose is 10 percent to 20 percent of the daily maintenance regimen.\(^7\) Follow-up frequency is contingent upon patient factors such as clinical condition and risk factors for abuse. At a minimum, pain monitoring should occur at each outpatient encounter or daily in the inpatient setting. In addition to education about safe and effective use of opioids, it is important to convey expectations and treatment strategies for managing adverse effects such as opioid-induced constipation.\(^7\)

While opioids are the mainstay of treating cancer pain, many other agents are used as adjuvants. Neuropathy is a common complication caused by both disease and treatment. Antidepressants, anticonvulsants and topical anesthetics may provide relief. Glucocorticoids are used to relieve complications of inflammation such as bone pain, nerve compression and bowel obstruction. Non-emergent bone pain may be palliated with bisphosphonates, hormonal therapy,
chemotherapy or radiation therapy. A referral to interventional care may be considered when pain is refractory, managed with intolerable adverse effects or when patients are unable to tolerate systemic therapies. Examples of interventional procedures include nerve blocks, regional infusion pumps, vertebroplasty, neural destructive procedures, neurostimulation and radiofrequency ablation. Finally, episodic and acute pain may require distinct management. Some procedures that cause pain and anxiety warrant prophylaxis. Examples include biopsy, bone marrow aspiration, radiation and placement of a central venous catheter. Pharmacologic strategies may include supplemental analgesics, local anesthetics, anxiolytics, sedatives or a combination of these agents. Integrative strategies may also be considered to help manage pain and care-associated anxiety, including physical therapy, cognitive behavioral training and faith-based counseling. Another scenario that may require distinct management is severe uncontrolled pain. In these cases, an oncolytic emergency must be discerned from non-emergent issues with emergencies encompassing the occurrence or imminent threat of bone fracture, epidural metastases, severe infection, obstructions, perforations or hemorrhage into a tumor. These events may require life-saving interventions such as surgery or blood transfusions. In addition to analgesics, other agents such as antibiotics and steroids may need to be rapidly initiated.

The onus is on pharmacists to ensure patients receive the safest, most effective drug therapy feasible. Challenges to this endeavor include underutilization of guidelines, misguided patient expectations, fractionated care and low adherence rates. Education and partnership with patients, providers and caregivers is essential for surmounting these obstacles. In collaboration with the care team, pharmacist involvement in cancer pain management can raise standards of care and improve quality of life for patients living with cancer pain.
References
