INTRODUCTORY LECTURES

# The Global Experience of Cancer Pain

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## Abstract

**Pain is a significant problem in patients with cancer. Pain occurs in approximately 50% of patients at some point during the disease process and in up to 75% of patients with advanced cancer. Total pain impacts quality of life domains including physical, psychological, social, and spiritual realms. Unfortunately, pain is underappreciated and undermanaged throughout the world. Lack of knowledge among healthcare professionals, inadequate pain assessment, fears of addiction, and beliefs that pain is an inevitable component of cancer are common barriers. Education about comprehensive pain assessment and optimal management strategies and discussions about belief systems regarding pain can assist to bridge the gap between suffering and comfort. Self-report is the gold standard for pain assessment. Gathering information about the location(s), intensity, quality and temporal factors is essential. Intensity should be quantified on a rating scale to determine the amount of pain and the degree of relief from interventions. Quality can be used to diagnose the specific pain syndrome. Temporal factors provide input about how the pain is experienced over time and can offer input into the pain management plan of care. For patients who cannot self-report pain, non-verbal assessment tools are available to aid in assessment. The World Health Organization's Analgesic Ladder provides a template for the management of cancer pain. For step 1, pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDS) and other nonopioid analgesics. As pain persists or increases, step 2 involves managing pain with select opioids for mild to moderate pain along with NSAIDS and nonopioid analgesics. Step 3 of the ladder is applicable to many cancer pain syndromes, and includes opioids for moderate to severe pain in conjunction with NSAIDS and nonopioids. This 3 step approach can be 80-90% effective. This polypharmaceutical employed with behavioral complimentary techniques are often employed to interrupt pain along the physiological pathways during transduction, transmission, perception, and modulation. Severe cancer pain that is not managed with the Step 3 approach, deserves special attention and unique strategies for control. When pain control is inadequate or if side effects are intolerable, a change of opioid or a change in the route of administration is recommended. Intraspinal analgesics can be trialed in patients who have intractable pain or intolerable side effects with systemic opioids. This route is especially helpful in neuropathic pain syndromes located at the trunk level or below. Opioid doses in all patients with intractable pain should be titrated judiciously for optimal relief with a balance of toxicity management. Other strategies for intractable pain should be investigated including nerve blocks and neuroablation. The overall goal for patients is to attain comfort with minimal side effects and optimal quality of life.**

**Keywords**: Cancer pain - QOL - World Health Organization's Analgesic Ladder - drug control

*Asian Pacific J Cancer Prev,* **11**, MECC Supplement, 7-12

## Introduction

Over 10 million people around the world are diagnosed with cancer per year, and pain is a significant problem in patients with cancer. Approximately one-third of patients undergoing cancer treatment experience pain and up to two-thirds with advanced disease. In response to this serious problem, the International Society for the Study of Pain (IASP) recently launched a "Global Year Against Cancer Pain" campaign to focus on the pain and suffering experienced by people with cancer (IASP, 2010). The significance of uncontrolled pain cannot be underscored. Pain is often associated with depression (Turner et al, 2005), fatigue and sleep disturbance (Roscoe et al., 2007), and decreased quality of life (Thong et al., 2009). This manuscript will discuss the global experience of cancer pain including the concept of "total pain," pain barriers, pain assessment, and pain management modalities including the management of pain crises.

## Total Pain

The concept of "total pain" was first introduced by Dame Cicely Saunders in the 1960s. Total or global pain involves the interplay of physical, psychological, social, and spiritual factors that constructs each patient's unique

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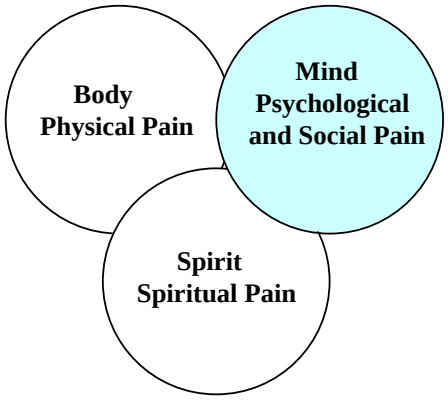


**Figure 1. The Concept of Total or Global Pain**

pain experience. Total pain reinforces the interconnectedness between mind, body, and spirit (Figure 1). Healthcare practitioners commonly focus on the physical pain; however pain is more than a physiologic process. Psychologically, pain can be described as dreadful, and reminds patients of the cancer and uncertainty of the future (Larsson & Wijk, 2007). Socially, patients may become isolated and even suppress pain to family members as a guard from family reactions (Larsson & Wijk, 2007). Spirituality can affect individual perception and intensity about pain, the significance of the meaning of the pain, and the acceptance of the medical treatment plan. If total pain involves physical, psychological, social, and spiritual domains, then management of pain should encompass all domains.

## Barriers

International recommendations on the assessment and management of pain are remarkably consistent and provide a sound foundation for practitioners around the world (Curtiss, 2004). According to the International Association of Nurses in Cancer Care, 90% of pain could be adequately controlled with standard measures. Unfortunately, a chasm exists between recommendations and reality, and patients around the world continue to suffer. Barriers exist that avert optimal management of pain including lack of knowledge of practitioners, myths and misconceptions of patients and families, and inadequate healthcare systems. One global barrier involves fear of addiction and confusion with the terms "tolerance, physical dependence, and addiction" (Table 1). Efforts are being made around the world to overcome barriers through provision of education to healthcare practitioners (IASP, 2010), patients, and families. For example, a meta-analysis of 15 studies examined patient-based educational interventions on pain outcomes (Bennett et al., 2009). Education improved patient knowledge and attitudes, and decreased average and worst pain intensity scores. Overall, a collective voice is needed to improve pain assessment and management around the world.

**Table 1. Definitions**

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|---|
| Tolerance: Tolerance is a state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time |
| Physical Dependence: Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist |
| Addiction: Opioid addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. |
| (American Academy of Pain Medicine, American Pain Society, & American Society of Addiction Medicine, 2001) |

**Table 2. Pain Assessment Domains**

| Domain | Pain Assessment | Components |
|---|---|---|
| Physical | | |
| | Location(s) | o Body Diagram |
| | | o Point and show area of pain |
| | Intensity | o "0 – 10" scale with "0" being no pain and "10" being the worst pain imagined |
| | | o Mild, moderate, severe |
| | | o Nonverbal pain scales |
| | Quality | o Descriptors about the pain: dull, sharp, shooting, radiating, numb |
| | Temporal factors | o Onset |
| | | o Duration |
| | | o Constant versus episodic |
| | | o Breakthrough |
| | | o Aggravating factors |
| | | o Alleviating factors |
| | Impact of pain | o Activities of daily living |
| | | o Function |
| | | o Other domains below |
| Psychological | | |
| | Psychological well-being | |
| | Prior psychopathology | |
| | Coping strategies (prayer, meditation, activities) | |
| | History of substance abuse | |
| Social | | |
| | Social functioning | |
| | Degree of isolation | |
| | Social support system | |
| Spiritual/Existential | | |
| | Cultural and/or religious beliefs related to pain and suffering | |
| | Spiritual practices used to manage or alleviate pain | |
| | Meaning of the cancer | |
| | Meaning of the pain | |
| | Spiritual support system | |

## Assessment of Pain

Adequate pain management begins with the assessment of the pain using a standardized assessment tool. Components of a pain assessment are included in Table 2 (American Pain Society, 2008; Middleton-Green, 2008). Psychological, social, and spiritual assessment tips are also included to reflect a "total pain" assessment. Practitioners should keep in mind that pain is a subjective experience; therefore, self-report is the gold standard. For the patient who cannot verbally report pain, nonverbal tools such as the Checklist for Nonverbal Indicators (CNPI) used in hospitalized adults and the Faces, Legs,

Arms, Cry, Consolability (FLACC) tool used in children are available through the City of Hope Pain Resource Center (www.coh.org) and within other references in the literature (Herr et al., 2006).

## Pathophysiological Pathways

The management of pain begins with an understanding of the pain pathway: transduction, transmission, perception, and modulation. Transduction initiates the pain response following a mechanical, thermal, or chemical injury. This initiates an inflammatory response resulting in the release of neuromediators such as prostaglandins, histamine, bradykinin, and substance P. Subsequently, an action potential occurs along the neuronal membrane. Transmission occurs as the action potential continues to the spinal cord and higher centers in the brain to the cortical level where perception of pain occurs. The brain then responds to the stimuli through modulation. Neurons release serotonin, norepinephrine, and endogenous opioid at the dorsal horn of the spinal cord in order to inhibit the transmission of pain impulses. Management of pain involves a polypharmaceutical and nonpharmacologic approach to interrupt the pain signal at all levels of the pathway and prevent pain input into the brain processing center.

## Pharmacologic Management of Pain

The World Health Organization (WHO) Analgesic Ladder provides a framework for the pharmacologic management of cancer pain. When used appropriately, pain can be adequately managed 80-90% of the time. Oral nonopioid analgesics are used in step one to control mild pain. As pain persists or increases, step two includes opioids for mild to moderate pain in combination with nonopioids. As pain persists or increases and becomes severe, step three includes opioids for moderate to severe pain along with nonopioids. Adjuvant or coanalgesics are used as needed for each step of the ladder. Well-established evidence supports the three step ladder interventions. Nine systematic reviews and 24 intervention trials demonstrate strong evidence for the use of NSAIDS, opioids, radionuclides, and radiotherapy while there is less consistent evidence for the use of bisphosphonates for pain or a painful event such as fracture (Lorenz et al., 2008). The nonopioid, opioid, and adjuvant analgesics are described below.

Non-opioids: Acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDS) are nonopioids used for cancer pain. Acetaminophen is often used as a first line agent in treating mild pain. The maximum dose is 4 grams daily, which includes all opioid and acetaminophen combination products. NSAIDS are useful in the management of mild to moderate pain, post-operative pain, bone metastases, and inflammatory pain syndromes such as lymphedema. The mechanism of action is blocking the production of cyclooxygenase and subsequent prostaglandin synthesis. Benefits of NSAIDS should be carefully weighed with potential adverse effects including gastrointestinal irritation, inhibition of platelet aggregation, and renal toxicity (American Pain Society, 2008) .

Opioids: Opioids, the mainstay of cancer pain management, exert analgesic effects by binding to opioid receptors at the dorsal horn of the spinal cord. Opioid receptors increase in density 24-96 hours following dorsal root ganglia stimulation, caused by inflammation or trauma. Table 3 includes the most commonly used opioids for cancer pain management. The primary opioid side effects include respiratory depression, sedation, constipation, urinary retention, and nausea and vomiting. Prophylactic management of constipation includes the use of a stool softener and bowel stimulant. Methylnaltrexone, that reverses opioid receptors in the gut, can be used for refractory constipation (Chamberlain et al., 2009).

Opioid Dosing and Titration: Knowledge of pharmacokinetic properties of opioids is essential in dosing and titrating to analgesic efficacy. Opioids should be initiated using the least invasive route and at lowest dose to effectively treat the pain. Titration can occur after maximum serum concentration is reached and titrated by 25-50% for moderate pain and 50-100% for severe pain. Controlled release or long acting opioids are recommended for constant pain and prevent peak and trough blood levels, thereby preventing high peak levels associated with immediate release opioids and related side effects such as over sedation (Thomas & von Gunten, 2003). Breakthrough pain, a transient increase in pain over a background of constant pain is common in many cancer pain syndromes. It is characterized by a rapid onset with severe intensity and is managed with opioids at a percentage of the baseline dose. For oral opioids, the breakthrough dose should be 10-20% of the 24 hour dose. For IV infusions, the bolus dose should approximate 50-150% of the hourly infusion rate. High bolus doses are used with hard to manage episodic or incident pain. Dose titrations should be 25-50% for moderate pain and 50-100% for severe pain (Clary & Lawson, 2009). For uncontrolled pain or side effects with one opioid, rotation to an alternative opioid is an option. The dose should be reduced to account for the lack of complete cross tolerance (Clary & Lawson, 2009).

Opioid rotation to the parenteral or intraspinal route is another option for uncontrolled pain. The intravenous (IV) route provides a rapid maximum concentration, and subcutaneous route is an alternative to IV with equal efficacy. Advantages over the IV route include less expense, a lower rate of infection, and no need for IV access (Justad, 2009).

## Adjuvants/Coanalgesics

Adjuvants or coanalgesics potentiate other analgesics, have independent pain relieving properties, or counteract side effects caused by the analgesic regimen. Adjuvants exert their effects through various mechanisms of action along the pain pathway. Some of the most commonly used adjuvants will be discussed. Corticosteroids are thought to block inflammatory mediators during transduction although their exact mechanism of action is unknown. They provide relief from visceral pain

**Table 3 Opioids Used in Cancer Pain Management**

| Opioid | Preparations | Comments |
|---|---|---|
| Morphine | Oral Controlled release (CR)<br>Immediate release (IR)<br>Oral solution<br>Rectal<br>Parenteral Intravenous (IV)<br>or subcutaneous (SC)<br>Intraspinal Preservative free (PF) | Opioid for comparison of other opioids<br>Variety of preparations useful when changing routes<br>Metabolites that can accumulate with renal compromise: morphine-3-glucoronide (M3G) counteracts analgesic effect and may be responsible for side effects, morphine-6-glucoronide is a potent analgesic metabolite |
| Oxycodone | Oral CR IR<br>Combination with acetaminophen / aspirin Oral solution | 1.5 times more potent than morphine<br>Parenteral preparation not available<br>No known active metabolites<br>CR has biphasal peak at 1 and 6 hours<br>Metabolized by CYP450 but implications unclear |
| Oxymorphone | Oral CR IR<br>Parenteral IV or SC<br>Rectal | 10 times stronger than IV morphine and 4 times stronger than oral morphine (Knotkova et al, 2009). Administer oral dose on an empty stomach; food increases the maximum concentration<br>Do not administer with alcohol<br>No CYP450 drug-drug interactions so consider in cases with polypharmacy issues. Contraindicated in moderate and severe hepatic impairment<br>Initiate with a low oral dose (5 mg) in patients with a creatinine clearance < 50 mL/min, mild hepatic impairment |
| Fentanyl | Transmucosal Lollipop/Pastille/<br>Transdermal patch (TD)<br>Parenteral IV or SC<br>PF for intraspinal use | Pharmacokinetics vary depending upon route:<br>oOral transmucosal fentanyl citrate (OTFC) an option for the mangement of breakthrough pain. Efficacy reported in 4 studies, 1 study reported that OTFC was superior to morphine (Zeppetella & Ribeiro, 2006)<br>o TD – 12 hour onset, 24-48 hour peak<br>o Parenteral – onset approximately 5 minutes IV, 10 minutes SC<br>Lipophilic opioid which may assist in global distribution of drug<br>Metabolized by p450 enzyme but clinical implications are not understood |
| Hydro-morphone | Oral IR CR<br>Rectal<br>Parenteral IV or SC<br>PF for intraspinal use | 5 to 7 times more potent than IV morphine; 4 times more potent than morphine (Knotkova et al, 2009)<br>CR currently available<br>Primary metabolite hydro-morphone-3-glucoronide (H3G) but little is known about its role<br>May be an option in patients with polypharmacy issues due to lack of CYP450 interaction (Pergolizzi et al., 2008) |
| Methadone | Oral<br>Sublingual (trials)<br>Rectal<br>Parenteral | High bioavailability Inexpensive<br>Long-acting in all forms but not controlled-release<br>Highly protein bound with long half-life allows for less frequent dosing but can cause potential for accumulation and toxicity<br>Large inter-individual variation in dosing<br>Metabolized by p450 with potential for drug-drug interactions<br>High affinity for mu-receptors and delta-receptors; animal models demonstrate N-methyl-D-aspartate (NMDA) antagonism with potential to manage neuropathic pain syndromes and prevent tolerance<br>Only skilled practioners should prescribe (Alford et al., 2006; Nicholson, 2007) |

syndromes such as ascites, and from nerve entrapment such as brachial or lumbosacral plexopathies (American Pain Society, 2008).

Anticonvulsants such as gabapentin and pregabalin, inhibit transmission of pain through nerve stabilization and are indicated for neuropathic pain syndromes. Gabapentin can be titrated to 4800 mg per day, unless the patient has renal compromise: 600 mg twice daily if glomerular filtration rate (GFR) 30-59, 300 mg twice daily for GFR 15-29, and 300 mg daily for GFR less than 15 (Hanlon et al., 2009). Absorption is dependent on the gastrointestinal transport system. Pregabalin follows a simpler dosing schedule, starting at 150 mg/day and escalating to 150-300 mg twice daily (McDonald & Portenoy, 2006).

Antidepressants, specifically tricyclic (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRI), are adjuvants, also used in the treatment of neuropathic pain. Tricyclic antidepressants can cause cardiovascular toxicity including orthostatic hypotension and heart block and should be used with caution, especially in the elderly. Less evidence exists for the use of SNRIs, but they may be favored because of their lower toxicity profile (McDonald & Portenoy, 2006; American Pain Society, 2008).

Bisphosphonates have become increasingly important in the management of pain from bone metastases. Over 30 randomized clinical trials report bisphosphonates

**Table 4. Pain Management Tips**

1. Conduct a global pain assessment on all patients.
2. If possible, determine the etiology of the pain so that strategies can focus on the source of pain.
3. Use a combination of nonopioids, opioids, and adjuvants as needed to control pain.
4. For elderly patients, start low and go slow, but efficiently for optimal comfort.
5. Use one opioid for both chronic pain and for breakthrough or acute episodes of pain.
6. Start with the simplest and most effective route of administration.
7. For long-acting opioids, titrate dosages by 25-50% for moderate pain and 50-100% for severe pain.
8. Keep breakthrough doses for oral medications at 10-20% of the 24 hour long-acting dose.
9. Use intravenous or alternative routes for pain crises.
10. For intravenous infusions, titrate hourly infusion rates by 25-50% for moderate pain and 50-100% for severe pain.
11. For bolus doses with intravenous infusions, keep bolus dose at least 50% of the hourly rate; higher bolus doses may be needed with severe incident pain.
12. Provide an adequate bowel regimen upon initiation of opioids that include a stool softener with a bowel stimulant.

Data from (American Pain Society, 2008; Ferrell et al., 2008).

provide some degree of pain relief in patients with bone metastases (Wong & Wiffen, 2009). There is a delayed effect; therefore, it is not a first-line therapy for pain.

## Nonpharmacological Pain Management

Nonpharmacological treatment modalities reinforce the need to address the total pain experience. Massage and transcutaneous electrical nerve stimulation are complimentary measures that can modify transduction of pain. Distraction, relaxation, and music therapy are modalities that can alter pain perception. In addition, the perceptual centers include the brain cortex that integrates previous experiences of pain, cognition, interpretation of pain, and emotions (Middleton-Green, 2008). Guilt, fear, and unresolved psychosocial and spiritual issues may influence pain perception (Hemming & Maher, 2005; Ferrell et al., 2008). Therefore, the total pain plan of care should include discussion of psychological, social, and spiritual beliefs that contribute to suffering.

## Intractable Pain Management

The majority of patients can be managed via the three step WHO ladder, but a subset of patients do not achieve ample relief of pain and require additional approaches. In addition, high opioid doses can lead to additional side effects such as tolerance, delirium, myoclonus, and hyperalgesia. Intraspinal analgesia using opioid and adjuvant combinations (e.g. bupivacaine, clonodine) or nerve blocks are options but are underutilized (American Pain Society, 2008; Jackson & Gaeta, 2008). One Scottish study showed that 8-20% of patients had pain indications that could potentially respond to anesthesiology approaches, but few patients were referred (Linklateret al., 2002). Clinicians should consider these options that can be more effective than traditional approaches alone.

Adjuvants such as N-methyl-D-aspartate (NMDA) antagonists can also be employed for intractable pain in attempt to decrease tolerance and address neuropathic pain challenges. Ketamine is an NMDA antagonist shown to alleviate pain in intractable and refractory situations. Administered at subanesthetic doses, it can be initiated at 0.1 mg/kg bolus doses and then converted to a subcutaneous or intravenous infusion. Opioids on board are usually dropped by 25-50% upon initiation of the ketamine and then titrated downward according to analgesic effect (Fine, 2005). Dextromethorphan is another NMDA antagonist although a trial that investigated the effect of morphine plus dextromethorphan found the combination not superior to morphine alone (Dudgeon et al., 2003). Lidocaine infusions can be used for intractable cancer pain, but efficacy, safety, and outcome studies are lacking (Fine, 2005).

## Palliative sedation

Rarely, pain cannot be controlled using aggressive titration protocols, alternative routes of administration, and other procedures such as neurolytic blocks. In such cases, palliative sedation can be offered to patients who desire this option. Barbituates, neuroleptics, and benzodiazepines are options that can be employed, usually via SC or IV infusion (Fine, 2005). The goal is to achieve comfort without postponing or hastening death.

## Summary

Around the world, pain is a deleterious symptom that is commonly associated with cancer. Uncontrolled pain can disrupt healing and can affect overall quality of life. Optimal management of pain requires a multifaceted approach. A comprehensive assessment should include not only physiological parameters but also “total pain” domains including psychological, social, and spiritual factors. A standardized assessment tool used at regular intervals facilitates the pain management plan that includes nonopioids, opioids, and adjuvant analgesics via the 3 step WHO analgesic ladder. Routes of administration should begin simple but may progress to parenteral and intraspinal routes as needed to control pain and minimize side effects. This step wise approach can optimize patient comfort and quality of life.

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