Cancer Pain: Etiology, Barriers, Assessment, and Treatment

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Cancer pain affects more than one in four patients with early-stage cancer, and approximately three out of every four patients with advanced disease according to recent statistics (Bennett et al. 2012)(Hearn et al.2003)(Van Den Beuken, 2007)(Higginson, 2010). Cancer pain may result from direct tumor invasion of local tissues, compression or invasion of nerves, metastasis into bone, visceral obstruction, or after disease directed primary therapy (i.e. chemotherapy, radiotherapy, or surgery). Clinicians may describe cancer pain as nociceptive (somatic), visceral, or neuropathic. Despite its classification system, cancer pain is often multifactorial and proven to be difficult to treat. Unfortunately, even into the 21st Century, undertreatment of cancer pain persists and cancer patients often site moderate to severe pain at some point in their disease process (Bennett et al. 2012)(Klepstad et al. 2002). Unrelieved pain impacts all dimensions of quality of life and profoundly influences the patient's ability to endure treatment, live as a cancer survivor, or live out their remaining time comfortably (Paice, 2011).

The WHO analgesic ladder serves as the mainstay of treatment for the relief of cancer pain in concert with disease-directed primary therapy and psychological and rehabilitative modalities. However, despite implementation of WHO analgesic guidelines, substantial obstacles to adequate pain relief persist. From patients' fear of addiction and physical dependence with opioids to the healthcare providers' reluctance to prescribe controlled drugs, barriers persist at multiple levels: patient, professional, and system-wide to achieve adequate pain control. Additionally, healthcare professionals are becoming increasingly aware of the importance of appropriate assessment and reassessment tools to monitor pain control but further education is essential. Once barriers to treatment have been addressed, and adequate assessment tools routinely adopted, physicians and nurses must be familiar with the array of medications available, their dosing, and side effect profiles to safely tailor a specific pain regimen to each patient's needs.

Herein we discuss the etiology of cancer pain and common terminology, highlight cancer undertreatment and barriers to effective relief, describe assessment tools commonly employed for comprehensive assessment of cancer pain, and provide an overview of the armamentarium of medications physicians may offer their patients.

Scope of the problem

Cancer pain has a prevalence of 25% for those patients newly diagnosed, 33% for patients undergoing active treatment, and greater than 75% for patients with advanced disease (Paice, 2011)(APS, 2008). These alarming statistics have not only caught the attention of the oncological community, but the World Health Organization (WHO) and the international pain community at-large (WHO, 2007). Factors influencing the development of chronic pain aside from the tumor burden itself reside in the cancer treatment modalities: surgery, radiation, and chemotherapy, and their effects on the body (Paice, 2011)(Sun V.et al.2008)(Ripamonti et al. 2012). Only half of cancer patients with chronic pain (whether from the tumor burden itself or sequelae of the therapeutic modalities), will receive adequate analgesia according to a systematic review of the literature (Deandrea S.et al. 2008). The WHO has cited the incidence of cancer to be over 12 million new cases in 2008 and may exceed 15 million by 2020. Thus, the magnitude of this issue cannot be overstated, and it is worthy of the medical community's focused attention.

Etiology of Cancer Pain

Cancer pain may result from tumor invasion into nerves, bones, ligaments, fascia, or soft tissue (Christo et al. 2008). Interestingly, certain types of cancer are associated with a higher prevalence of chronic pain. For example, pancreatic (44%) and head and neck cancers (40%) are more prevalent than leukemia (5%) (Brescia, 2004)(Burton, 2007)(Christo, 2008). Literature supports that although the majority of cancer pain may result from the tumor burden itself, 25%-33% of pain experienced by cancer patients may be attributed to cancer-related treatments (surgery, radiation therapy, chemotherapy, etc.) (Bonica, J et al. 1990)(Christo et al., 2008)(Paice, 2011). For example, surgical procedures, such as, post-chemical pleurodesis, pleural drainage, or biliary dilatation may lead to chronic pain. Surgery may also result in pain states such as post-thoracotomy pain, post-amputation (phantom limb) pain, or Complex Regional Pain Syndrome (CRPS). Radiotherapy may cause acute post-radiation complication including mucositis, esophagitis, and acute myelopathy; whereas chronically it may result in osteoradionecrosis, brachial and lumbosacral plexus fibrosis, skin necrosis, muscle fibrosis, and post-radiotherapy myelopathy. Additionally, chemotherapy may be associated with septic bone necrosis (Caraceni, 2012)(Portenoy, 2010). Several classes of chemotherapeutic agents such as alkaloids, platinum based compounds, and the antimitotics, are known to contribute to peripheral neuropathies (Christo et al. 2008)(Polomano et al., 2006). Table 1 summarizes different etiologies of cancer pain.

Table 1. Etiologies of Cancer Pain

- Direct Tumor Invasion
  - Bone, Ligament, Fascia, Nerve, Soft Tissue
- Tumor Metastases
  - Spinal cord, Bone, Abdominal Viscera, Thorax
- Interventions
  - Surgery
    - Postamputation phantom pain; Post-thoracotomy pain; Postmastectomy pain
  - Radiation
    - Osteoradionecrosis; Plexopathies; Myelopathy

- ○ Chemotherapy
  - ▪ Osteonecrosis; Paresthesias; Myalgias; Peripheral neuropathy
- ○ Hormonal Therapy
  - ▪ Arthralgias; Osteoporotic compression fractures

Cancer pain is an umbrella term used to describe pain of mixed etiologies and mechanisms. To effectively treat cancer pain, one must understand the etiology given that etiologies with different mechanisms will respond better to certain therapies. For example, nociceptive pain may best respond to opioid management whereas neuropathic pain may best respond to membrane stabilizer medications such as gabapentin. Clinicians may categorize cancer pain as nociceptive (somatic), visceral, or neuropathic (Christo, 2008). Nociceptive pain is associated with tissue injury whether from surgery, trauma, inflammation, or tumor. The pain is caused by stimulation of pain receptors in cutaneous and deeper musculoskeletal structures. It is often proportional to the degree of nociceptor activation. Nociceptive may be synonymous with somatic pain and is described as well localized, stabbing, throbbing, or pressure-like and arises from direct injury to bones, joint, muscle, skin, or connective tissue. Examples of nociceptive (somatic) pain often include metastatic bone pain, postsurgical incisional pain, and musculoskeletal inflammation and spasm. Visceral pain is described as poorly localized, gnawing, diffuse, cramping, and may be associated with distension of organs, nausea, vomiting, and sweating. This type of pain arises from organ damage or tumor infiltration, compression, or distortion of organs within the pelvis, abdomen, or thorax. The pain may be referred to superficial locations that are distant from the affected organ. Lastly, neuropathic pain is described as tingling, burning, electrical or shooting pain. This type of pain is invariably associated with sensory changes caused by injury to the central or peripheral nervous system. It may be directly related to the malignant disease, such as tumor infiltration of peripheral nerves, plexi, or spinal cord. Neuropathic pain also may arise from efforts to treat the disease, such as surgery, radiation therapy, chemotherapy, or drug-induced neuritis (Le Bel, 2002)(Foley et al. 1998)(Christo et al. 2008). Table 2 summarizes the different types of cancer pain.

Table 2. Types of Cancer Pain

- • Nociceptive/Somatic: well localized, stabbing, throbbing, pressure
  - ○ Tumor invasion into bone
  - ○ Pathologic fracture
  - ○ Postsurgical incisional pain
  - ○ Musculoskeletal inflammatory pain
- • Visceral: poorly localized, gnawing, diffuse, cramping
  - ○ Tumor invasion into organs
  - ○ Obstruction (i.e. biliary, intestinal)
  - ○ Organ rupture (i.e. bowel, bladder)
  - ○ May have referred pain distant from affected organ
- • Neuropathic: burning, tingling, shooting, electric
  - ○ Tumor compression of plexi
  - ○ Tumor invasion into peripheral nerves or nerve roots
  - ○ Tumor invasion into spinal cord
  - ○ Chemotherapy induced neuritis (i.e. vincristine, platinum, paclitaxel)

o Radiation-induced nerve injury
o Post-surgery (i.e. post-thoracotomy pain, post-amputation, CRPS)

Barriers to Treatment

Barriers to achieving adequate cancer pain relief have been studied and broadly classified into patient, professional, and system-wide obstacles (Paice, 2011)(Baltic, 2002)(Lasch, 2002)(Payne, 2000)(Ward, 2001)(Christo, 2008). The barriers to optimum pain relief were first introduced in 1994 by the Agency for Health Care Policy and Research. According to their guidelines, the patient maintains a central role in his/her pain treatment. For instance, patients historically have demonstrated a reluctance to communicate pain for fear of opioid addiction and physical dependence, concerns about adverse effects of medications, fear of distracting physicians from treating the cancer, fear of disappointing their physician, and fears that worsened pain signifies progression of disease (Gunnarsdottir, 2002)(Ward et al 1994)(Ward et al 1993)(Miaskowski, 2001)(Pargeon, 1999). However, the literature has demonstrated that overcoming these barriers is possible. Programs have emerged that support the use of pain assessment tools, focused discussions to dispel misconceptions about the medications (i.e. opioids), and more open and frequent communication regarding options for treatment and to evaluate the success of therapies (Miaskowski, 2004)(Christo, 2008)(Christo, 2008). The presence of a cancer pain or palliative service as an integrated facet to the patient's care team helps aid in addressing patient barriers earlier (Akashi et al. 2012).

Ward and colleagues in their survey of 270 patients with cancer investigated reasons that patients may be reluctant to report pain or use pain-relieving medications (Ward, 1993)(Tolle, 2000). Almost 80% of patients cited fear of addiction with pain medications as a prime concern, and up to 85% reported believing that side effects of pain medications could not be mitigated. Approximately 60% of patients stated that a choice needed to be made between treating their pain and treating their disease. An equally high percentage felt that pain medication should be reserved for severe pain only; otherwise, it it may be ineffective when needed. Finally, nearly half of the patients feared annoying their physician if they constantly complained of pain (Ward et al, 1993)(Christo, 2008). It is humbling for clinicians to know that such widespread misconceptions exist, and this emphasizes the need for communication in this area.

Professional obstacles also persist to achieving cancer pain relief. Physicians are often reluctant to prescribe controlled substances such as opioids. Many doctors feel that managing pain with controlled substances leads to tedious documentation and entails frequent prescription refills. Moreover, physicians have felt that, in specific that opioid prescribing expose them to intense regulatory scrutiny (Phillips et al. 2000). Similarly, nurses may also share concern about administering opioids to cancer patients secondary to their lack of familiarity with side effect profiles, titration schedules, and escalating dosages.

Healthcare workers understandably fear the adverse effects associated with opioids, namely respiratory depression. Opioids may affect the rate of respiration and, to a lesser extent the depth of respiration. Data from studies on mice indicate that both the analgesic and respiratory depressive features of morphine are linked to the mu opioid receptor (Dahan, 2002)(Romberg, 2003) in a dose dependent manner. Some research studies support the notion that respiratory depression may occur in human patients irrespective of the severity of their pain (Dahan, 2004). The literature, however calls this theory into question and clinical reports indicate that respiratory depression rarely precedes analgesia when administering opioids to relieve chronic pain. In other words, if a patient feels excruciating pain, one may safely assume they are not at risk of respiratory depression. With this conflicting data, where does this leave the clinician? Needless to say, a physician must always feel comfortable and safe with the medications prescribed. Thus, serious adverse effects of opioids can be reduced via attention to medication dose, methodical titration, and carefully prescribing both long acting, and short acting medications for breakthrough pain. Furthermore, clinicians should be

comfortable relying upon adjuvants when necessary to maximize analgesic benefit and minimize risk. To the prescribing clinician, being mindful of the co-administration of psychoactive substances (i.e. benzodiazepines, barbiturates, or other opioids) or the patient's consumption of other respiratory depressants (i.e. alcohol) necessitates vigilant attention to the respiratory depressant effects of opioids (Christo, 2008).

Another professional barrier is the incomplete understanding by physicians and nurses regarding addiction, tolerance, and physical dependence with opioids. Because many clinicians lack this understanding and excessively fear addiction, many patients suffer with inadequately treated pain. The American Society of Addiction Medicine defines addiction as a "primary, chronic, neurobiologic 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" (ASAM, 1998).

Patient behaviors suggestive of opioid addiction may include an inability to take medications according to a mutually agreed upon schedule, taking multiple doses together, and frequent reports of lost or stolen prescriptions. Other red flags include doctor shopping, increased patient isolation from family and friends, or use of non-prescribed psychoactive drugs in addition to prescribed medications (ASAM, 1998). Table 3 demonstrates warnings signs practitioners may heed when they suspect a patient is struggling with opioid addiction.

Table 3. Warning signs of Addiction among Patients Treated with Opioids

- Inability to take medications according to an agreed upon schedule
- Taking multiple doses together
- Frequent reports of lost or stolen prescriptions
- Doctor shopping
- Increased patient isolation from family/friends
- Frequent emergency room visits for opioid medication
- Missed follow-up visits
- Use of non-prescribed psychoactive drugs in addition to prescribed medications
- Use of opioids for purposes other than analgesia
- Non-compliance with non-opioid treatments
- Insistence on rapid-onset formulations/routes of administration
- Reports of no relief whatsoever by any non-opioid treatments
- Unexpected toxicology screen results

Patients who are addicted to opioids may demonstrate persistent sedation due to overuse; functional impairment; psychological manifestations such as irritability, apathy, anxiety, or depression; or adverse legal, economic or social consequences (ASAM, 2001) Common and expected side effects of the medications, such as constipation or sedation due to use of prescribed doses are not viewed as adverse consequences related to addiction.

No single event is diagnostic of an addictive disorder. Rather, the diagnosis is made in response to a pattern of behavior that usually becomes more clear over time (Portenoy, 1990)(Sees, 1993). Regrettably, overestimation of addiction in cancer patients treated with opioids has led to widespread undertreatment of pain in this population (McQuay, 1999). It is difficult to interpret the result of many studies designed to estimate prevalence of addiction in cancer patients on long-term opioid therapy because few studies exist and many fail to clearly define the terms used to evaluate addiction. However, evidence thus far makes a compelling argument that addiction or 'problematic opioid use' ranges in prevalence from 0.2% – 7.7% in cancer patients (Macaluso, 1998)(Passik, 2000) (Passik, 2000)(Schug, 1992). The published data, although sparse suggests that cancer-pain patients should not be undertreated due to an unsubstantiated fear of addiction. In chronic non-

malignant pain patients, the risk of addiction requires continuous monitoring during the course of treatment with opioids. As the longevity of cancer patients grows due to improvements in chemotherapy and other antineoplastic agents, their pain conditions will become longer-lasting and in fact, may mimic those of the chronic, non-malignant pain population receiving opioid therapy. Therefore, it seems reasonable that cancer patients who receive opioids for chronic treatment should be monitored for safe use with strategies such as urine drug monitoring, opioid agreements, and pill counts.

As Caraceni et al. describes, a great confusion about the terms [tolerance, physical dependence, and addiction/psychological dependence] on the part of physicians, nurses, patients, and their families has helped to slow down the correct use of opioid analgesics (Caraceni, 2012). To optimize opioid therapy, the specialist must clarify these terms for the healthcare professionals, patients, and family members alike. As defined by the American Society of Addiction Medicine, tolerance is "a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time" (ASAM, 2001). In other words, increased quantities of a drug (i.e. opioid) are required to produce the same level of effect (i.e. analgesia). Physical dependence may be defined as "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 dug, and /or administration of an antagonist" (ASAM, 2001). In simpler terms, physical dependence is the onset of withdrawal symptoms after an abrupt reduction of dosage or administration of an opioid antagonist (naltrexone). As a precaution, Caraceni et al., states that any patient should be considered physically dependent after regular treatment with an opioid drug for more than a few days (Caraceni, 2012). Psychological dependence is a behavioral and psychological syndrome characterized by loss of control over drug use and compulsive continuous use despite damage caused to oneself and others.

Most specialists in pain medicine and addiction medicine agree that patients treated with prolonged opioid therapy usually develop physical dependence and tolerance, but do not usually develop addictive disorders or psychological dependence. Tolerance to respiratory depression, sedation, and nausea develop rapidly whereas tolerance to constipation rarely occurs. Addiction, unlike tolerance and physical dependence, is not a predictable drug effect, but represents an "idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals" (ASAM, 2001). Addiction is recognized by the observation of characteristic features including impaired control, craving and compulsive use, and continued use despite negative physical, mental, and/or social consequences and has never been demonstrated in patients with advanced cancer (Caraceini, 2012) despite this fear.

A final barrier to cancer pain control involves system-related barriers. Legal and regulatory structures that interfere with the provision of optimal care, such as inadequate reimbursement for pain services serve as an example. (Agency for Health Care Policy, 1994). The Institute of Medicine and the National Cancer Policy Board have continued to document and emphasize the importance of system-related barriers in preventing quality pain management (Gee, 2003)(National Institutes of Health, 2002). System-related barriers also include a lack of access to pain medications, particularly in minority neighborhoods or for those who are poor. Several studies have documented the inequalities that persist for those with financial burdens or for minority patients who have less access to pain treatment (Ezenwa, 2006)(Green, 2003)(Paice, 2011). Comprehensive cancer teams that establish pain policies can circumvent several of these system barriers (Sun, 2007).

Pain Assessment Tools

The ability to accurately assess pain is indispensable to the management of cancer patients. A thorough patient assessment includes detailed history, physical and neurological examination, and pain assessment tools (Carecini, 2012). Key points to focus on in the history include the location, quality, duration, time course, and intensity of the pain as well as exacerbating or alleviating factors and whether the pain radiates or is referred to other locations. Often, cancer patients have multiple

sites of pain, and thus the sites should be accurately reported for a complete clinical picture. Pain treatment is mostly guided by intensity. Intensity can be assessed using a variety of tools including the Visual Analog Scale (VAS), numerical or verbal scale, or via multidimensional questionnaires (Carecini, 2012). The main intensity scales are the Numerical Rating Scale (NRS) which usually goes from 0 to 10 (with 0 being no pain and 10 being the worst pain imaginable), Visual Analog Scales (VAS), and Verbal Rating Scales (VRS) (Caraceni, 2001). .

The 0-10 NRS seems to have a common meaning even in different cultures and can be presented to the patient as a simple question: "On a scale of 0-10, with 0 as no pain and 10 as the worst pain you can imagine, at what number do you rate your pain?" In contrast, the VAS is presented as a 100-mm straight line with the extremes defined by descriptors such as "no pain" and "worst possible pain". Patients must mark on the line the point corresponding in their opinion to the severity of the pain. The score is calculated in millimeters, from the minimum severity to the point marked by the patient. VRS uses adjectives to describe the level of intensity of the pain (Caraceni, 2001)(Caraceni, 2012)(Portenoy, 1989). Other resources are available for a multidimensional assessment of cancer-related pain, such as the McGill Pain Questionnaire and the Brief Pain Inventory. Both are valid and reliable but their role remains confined to clinical trials.

It is important to note that whenever conducting pain intensity measurements, it is best to assess over a defined time period (i.e. last 24 hours, or over the past week), and it should always be made clear whether the intention is to measure the average pain or the worst pain experienced. These parameters provide context to the scores and make the results more meaningful. Furthermore, pain at rest and pain on movement (or acute exacerbations) should be assessed separately. The regular self-reporting assessment of pain intensity with the help of validated assessment tools is important in constructing effective and individualized treatment.

As Ripamonti et al. details, the intensity of pain and treatment outcomes should be regularly assessed using VAS, VRS or NRS (Ripamonti, 2012). Moreover, in older adults or those with limited communication, there is no evidence that pain-related suffering is any less severe, and observation of pain-related behaviors and discomfort (i.e. facial expression, body movements, verbalization or vocalization) can be an alternative strategy for assessing the presence of pain (but not intensity) (Kaasalainen et al 2007)(Gordon 2005)(Van Herk 2007)(Am Geriatric Soc., 2002). For patients who may experience impaired mental status, whether at baseline or secondary to progressive disease, the pain assessment can be greatly simplified by using a minimum verbal scale with few answers, such as "no", "a little", "a lot", "very much" to assess pain intensity (Caraceni et al., 2005).

In addition to patient self-assessment tools, the National Comprehensive Cancer Network (NCCN) published a comprehensive pain assessment guideline in 2010. .

As pointed out by the NCCN Comprehensive Pain Assessment, assessing psychosocial distress is essential because it is strongly associated with cancer pain (Zaza et al, 2002). In fact, psychological distress may amplify the perception of pain-related distress and similarly, inadequately controlled pain may cause substantial psychological distress.

Available Pain Medications

Pharmacological management is the mainstay of cancer pain treatment. Appropriate use of non-opioids, opioids, and adjuvant analgesics, along with a variety of anticancer therapies allows for great strides in managing cancer-related pain if appropriately applied. Before physicians discusses mainstay pain medications, adjuvants, and potential interventional procedures, it is important to educate the patient that pain may originate at any stage of the disease process, during and after diagnostic interventions, or related to anti-cancer treatments. Patients should be actively involved in managing their pain and encouraged to communicate freely with the physician and/or nurse about their suffering, the efficacy of therapies, and the side effects experienced (Reid et al, 2008).

Moreover the patient should be a welcomed member of the team, given that patient involvement has lead to improved outcomes in pain control (De wit et al., 1997)(Ripamonti, 2012).

Primary Therapies: Before we explore the wide array of medications that are offered, their mechanisms of action, details for use, and adverse effects, it is important to note that specific primary therapies may provide significant benefit to the cancer patient and are often given concurrently with medical management. These procedures may enhance a patient's function, longevity, and comfort.

Vertebroplasty: This procedure involves the injection of methylmethacrylate into a pain-sensitive vertebral body under radiographic guidance. The active agent stabilizes bony metastasis by solidifying the lesion and can achieve rapid resolution of pain with restoration of spine stability in 1-3 days (Fourney et al., 2003). Physicians trained in this technique primarily treat cancer patients with osteolytic lesions of the vertebral body who do not have disruption of the posterior body wall, vertebral body collapse, and suffer from severe pain. It is very important that the posterior body wall of the vertebral body is not compromised since methylmethacrylate could enter the spinal canal and lead to irreversible paralysis.

Surgery: Surgical intervention and tumor de-bulking can be invaluable in relieving painful symptoms from hollow organ obstruction, neural compression, and unstable bony structures (Krouse, 2004)(McCahill 2002). When cancerous conditions induce pain from obstruction of the esophagus, colon, biliary tract, or ureters, stenting of these structures may offer needed relief (Amersi, 2004)(Homs, 2004).

Radiotherapy: Substantial data support the effectiveness of radiotherapy in reducing the pain associated with bone metastases, epidural neoplasm, and headaches caused by cerebral metastases (Nielsen, 1998)(Christo, 2008)

Chemotherapy: There is a pervasive belief that an inverse correlation exists between cancer shrinkage from chemotherapy and analgesia. Although there is virtually no data to illustrate the specific analgesic benefits of chemotherapy (Bang, 2005) there are reports of pain reduction with tumor shrinkage (Burris et al. 1997).

Antibiotics: When pain is a manifestation of infection, antibiotics can serve an analgesic role. For instance, antibiotics are essential in treating cellulitis, pelvic or skin abscesses, and chronic sinus infection. Pain may also dissipate when empiric treatment of occult infections is initiated with antibiotic therapy. It is important to bear this in mind since many cancer patients will become neutropenic as cancer progresses or through treatment, and they have an increased susceptibility to infection as their innate immune defenses weaken.

WHO Cancer Pain "Ladder"

The World Health Organization (WHO) analgesic ladder serves as the cornerstone of treatment for the relief of cancer pain in concert with tumoricidal, surgical, interventional, chemo/radiotherapeutic, psychological, and rehabilitative modalities. This multidimensional ladder offers the greatest potential for maximizing analgesia and minimizing adverse effects. Optimistic studies site that 70-90% of cancer pain may be relieved when clinicians apply the WHO ladder appropriately (Jadad et al., 1995)(Ventafridda, 1987). The introduction of the WHO 3-step analgesic ladder in 1986 provided a concrete tool for physicians worldwide to use in combating cancer pain (Zech, 1995). More specifically, it provides a step-wise introduction of drugs of increasing strength as pain severity increases.

The stepwise approach to using pain relieving medications suggests that clinicians begin with a non-opioid (such as an NSAID or acetaminophen) and/or adjuvant. As pain persists or increases to

an intolerable level, the clinician may progress to an opioid for mild to moderate pain in concert with non-opioid medications and/or adjuvants. As pain persists, or increases opioids for moderate-to-severe pain may be utilized. WHO advises that clinicians use acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for mild pain (step 1); combination products, such as acetaminophen or aspirin plus codeine, hydrocodone, propoxyphene, or oxycodone, for moderate pain (step 2); and morphine, hydromorphone, oxycodone, methadone, or transdermal fentanyl for severe pain (step 3). In practice, new opioid formulations that include sustained-release preparations of codeine, oxycodone, morphine, fentanyl, buprenorphine, or oxymorphone are attractive for moderate to severe pain. Generally, pain is more effectively controlled if the clinician carefully titrates the analgesic dose and timing interval while simultaneously assessing and managing side effects (Quigley et al 2005)(Twycross et al 2001). Some practitioners have moved to an algorithm-based approach for treating cancer pain (Miaskowski 2005) and other clinicians have incorporated in interventional/procedural "fourth step" to the ladder. Algorithm-based approaches for treating cancer pain are another method for managing uncontrolled cancer pain as outlined by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

Irrespective of the specific strategy employed, an overview of the typical therapies to consider for the treatment of cancer pain is essential.

Nonopioid Therapy / Over-The-Counter-Agents

The WHO analgesic ladder recommends non-opioids beginning at step 1. These medications are useful in the management of mild to moderate pain and their continuation through step 3 is an option after weighing a drug's risk and benefits in individual patients. The two prime agents include the NSAIDs and acetaminophen. Both types have a "ceiling effect" or maximum therapeutic dose beyond which no further benefit is achieved and at which the risk of toxicity increases.

Acetaminophen: Acetaminophen is analgesic and antipyretic but not anti-inflammatory (Watson, 2000)(Paice, 2011). Clinicians traditionally have combined this agent with short-acting opioids if initial therapy is unsuccessful. The benefit of combining acetaminophen with opioids is the reduction in amount of opioid required for analgesia and theoretically the opioid-induced adverse effects (i.e. nausea, vomiting, pruiritis, constipation, and sedation). Healthcare providers must be mindful of the risk of acetaminophen hepatotoxicity at sustained doses of 4 grams per day in adults (Makin, 1995)(Schiodt, 1997) and note that a pending recommendation exists to limit the toxic dose to 3 grams per day. In fact, new attention has been focused on the relatively limited efficacy and significant adverse effects of this agent, particularly hepatic and renal toxicity (Am Geri Soc, 2009)(Israel, 2010). This concern is compounded by the inclusion of acetaminophen in a variety of prescription opioid preparations (i.e. hydrocodone or codeine) as well as in a wide selection of over-the-counter products. Of additional concern in those receiving cancer chemotherapy are case reports of interactions between anticancer agents and acetaminophen leading to hepatic toxicity (Ridruejo, 2007). Reduced doses of 2000 mg/day or the avoidance of acetaminophen is recommended in the face of renal insufficiency or liver failure, and particularly in individuals with a history of significant alcohol use (Swarm, 2010).

NSAIDs: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce inflammatory pain caused by cancer by blocking the biosynthesis of prostaglandins, inflammatory mediators that initiate, cause, intensify, or maintain pain. They have a well-established role in treating mild cancer pain as monotherapy and in conjunction with opioids in reducing moderate to severe pain (Grond, 1991)(McNicol, 2004). Like acetaminophen, NSAIDs offer the benefit of an opioid-sparing effect (Mercadante, 2002)(Mercadante, 1999). The nonselective NSAIDs, such as aspirin inhibit the conversion of arachidonic acid to prostaglandins, however; their lack of selectivity for cycloxygenase predispose to gastrointestinal ulceration, renal dysfunction, and impaired platelet aggregation as a result of cycloxygenaes-1 (COX-1) inhibition (Rainsford, 2007) (Simon, 2002). The cycloxygenase-2 (COX-2) enzymatic pathway is induced by tissue injury or other inflammation-inducing conditions. When using COX-2 selective agents, there is a reduced risk of gastrointestinal

erosion and bleeding; however this advantage may diminish after 6 months of use (Shi, S.,2008). COX-2 selective inhibitors, carry a risk associated with cardiovascular events, such as myocardial infarction, and cerebrovascular complications such as stroke with prolonged use (Scott, 2007) (Kerr, 2007) (Juni, 2002) (Simon, 2002). In cancer, NSAIDs are useful in the treatment of inflammatory-mediated pain and bone metastases. NSAIDs cause minimal nausea, constipation, sedation or adverse effects on mental functioning. Therefore, depending on the cause of pain, NSAIDs may be useful for the control of moderate to severe pain, usually as an adjunct to opioid analgesic therapy (McNicol, 2005). The addition of NSAIDs to opioids has the potential benefit of reducing the opioid dose when sedation, obtundation, confusion, dizziness or other central nervous system effects of opioid analgesic therapy alone become burdensome.

Decreased renal function and liver failure are relative contraindications for NSAID use. Platelet dysfunction or other potential bleeding disorders, common due to cancer or its treatmentcontraindicate use of the nonselective NSAIDs due to their inhibitory effects on platelet aggregation, with resultant prolonged bleeding time. Proton pump inhibitors or misoprostol can be given to help prevent gastrointestinal bleeding (Bhatt, 2008)(Schlansky, 2009). Thus in cancer patients, it is important to be mindful of their liver and renal status, thrombocytopenia, and whether they are susceptible to gastrointestinal bleeding. Care should be taken when using NSAIDs in the neutropenic population because the antipyretic and anti-inflammatory properties may mask signs and symptoms of infection.

Adjuvant Therapies (Co-analgesics): Adjuvant medications include non-opioids that confer analgesic effects in certain medical conditions such as the treatment of painful diabetic neuropathy or postherpetic neuralgia. The evidence for adjuvant effectiveness often is derived from well-conducted studies in the nonmalignant pain population rather than the cancer pain population. However, since the pathologic development of neuropathic pain is assumed to be similar in both cancer and non-cancer patients, it may be extrapolated that such agents may successfully treat neuropathic pain equally in both groups. Medications including antidepressants, anticonvulsants, corticosteroids, topical local anesthetics, bisphosphonates, and radiopharmaceuticals are included among the group of agents viewed as adjuvants and may be considered off-label.

Antidepressants: Antidepressants offer analgesic effects independent of their antidepressant effects (McQuay 1996)(Sindrup 1999). The strongest level of evidence for analgesic efficacy exists for the tricyclic antidepressants (TCA) (McQuay 1996). Tricyclic antidepressants providee analgesia through inhibition of the reuptake of norepinephrine and serotonin. Studies conducted to-date for neuropathic pain (i.e. diabetic neuropathy) demonstrate that TCAs provide a clinically relevant effect (Finnerup, 2010) and have been cited as a first-line therapy for neuropathic pain. Like all medications, it is important to review the dose limiting side effects. Cardiac arrhythmias, conduction abnormalities, narrow-angle glaucoma, and clinically significant prostatic hyperplasia are relative contraindications to TCAs. Their sleep-enhancing and mood-elevating effects may be of benefit. Examples of TCAs include nortriptyline and amitriptyline. Serotonin-norepinehrine reuptake inhibitor (SNRI) agents have been shown to also be effective in relieving neuropathic pain, including venlafaxine and duloxetine (Durand, 2002)(Tasmuth, 2002). An added advantage is that the SNRIs can treat hot flashes which may occur particularly in breast cancer patients undergoing hormonal therapy. It is worth mentioning an important drug-drug interaction between tamoxifen and CYP 2D6 inhibitors, including duloxetine. Concomitant use reduces the bioavailability of tamoxifen, potentially limiting survival (Goetz, 2007). There remains little support for the analgesic effect of SSRIs (Finnerup, 2010).

Anticonvulsants: There are two anti-epileptic drugs commonly employed for the treatment of cancer pain: gabapentin and pregabalin. Gabapentin and pregabalin are voltage-gated calcium channel blockers. These medications are effective for the treatment of neuropathic pain, commonly described as shooting, electrical, tingling, burning sensations and is regarded as first-line for treatment (Backonja, 1998)(Bennett, 2004)(Rice, 2001)(Dworkin, 2003)(Freynhagen, 2005). Both of these anti-epilepsy drugs have undergone extensive testing in many noncancer neuropathic

syndromes and yield a clinically significant effect (Finnerup, 2010)(Baron, 2008). The most commonly reported adverse effects by patients include dizziness and fluid retention. Other anti-epileptic medications, including topiramate, levetiracetam, and lamotrigine have been reported to successfully treat neuropathies; however, further studies need to be conducted. These agents are used often in combination with opioid therapy, particularly when pain is moderate to severe.

Corticosteroids: These drugs represent a widely used group of adjuvant therapies for cancer pain (Rousseau 2001) and can relieve pain syndromes, including plexopathies and pain associated with stretching of the liver capsule due to metastases (Wooldridge, 2001). They have also been used to treat increased intracranial pressure headache, superior vena cava syndrome, acute spinal cord compression, metastatic bone pain, and symptomatic lymphedema. Dexamethasone is the drug of choice given its low mineralcorticoid effect and consequent reduction in risk of Cushing's syndrome. Corticosteroid mechanism of action is principally through inhibiting prostaglandin synthesis, and also reducing neural tissue edema (Ettinger 1988)(Watanabe 1994). The standard dose is 4-24mg/day and can be administered once daily due to the long half-life of this drug (Americ. Pain Soc. 2008) (Jacox et al, 1994). Doses as high as 100 mg may be given with severe pain crises (Rousseau, 2001). It is important to remember that intravenous bolus doses should be given slowly, to prevent uncomfortable perineal burning or itching which is very unpleasant for the patient.

Local Anesthetics: Painful lesions of the mucosa and skin may respond to lidocaine preparations. For instance, patients find that viscous lidocaine eases the discomfort associated with oropharyngeal ulcerations, though the risk of aspiration and dysphaiga from anesthesia should be considered since the numbing effect can inhibit airway protective reflexes. Both gel and patch versions of lidocaine have been shown to reduce the pain of postherpetic neuralgia and cancer-related pain (Ferrini, 2004)(Fleming, 2009). Local anesthetics exert their analgesic effect by inhibiting the movement of ions across the neural membrane (Ferrini, 2004). Intravenous lidocaine may be administered as a continuous infusion to reduce intractable neuropathic pain for patients in inpatient palliative care and home hospice settings (Ferrini, 2004). Other local anesthetic routes include epidural or intrathecal administration, and these may be combined with an opioid for enhanced benefit.

NMDA Antagonists: The most commonly used NMDA antagonist is ketamine. Specifically, NMDA antagonists block the binding of glutamate and other excitatory amino acids in the spinal cord. Ketamine can also be provided through a variety of routes, like local anesthetics. Ketamine may be provided through the oral, intravenous, subcutaneous, intranasal, sublingual, topical, epidural, or intrathecal route. A Cochrane review found insufficient trials to determine its safety and efficacy in relieving cancer pain; however, case reports and small studies suggest that intravenous or oral ketamine can be used in adults and children with cancer for the relief of intractable neuropathic pain or to reduce opioid doses (Bell, 2003). It is important to keep in mind the undesirable effects of ketamine including hallucinations, and unpleasant cognitive sensations; however, patients respond well to intravenous benzodiazepine (i.e. midazolam) which can curtail these effects.

Bisphosphonates: Bisphosphonates inhibit osteoclast-mediated bone resorption and alleviate pain related to metastatic bone disease and multiple myeloma (Wong, R., 2002)(Walker, 2002) (Berenson et al, 1996)(Bloomfield, 1998). Pamidronate disodium has been shown to reduce the pain, hypercalcemia, and skeletal morbidity associated with breast cancer and multiple myeloma (Groff, 2001)(Lipton, 2000). Dosing is generally repeated every 4 weeks and the analgesic effects occur in 2-4 weeks. Despite these experiences, a combined analysis of 2 randomized, controlled trials of pamidronate in men experiencing pain due to prostate cancer failed to demonstrate any pain relief or prevention of fractures (Small, 2003). Zoledronic acid has also been shown to relieve pain due to metastatic bone disease, with at least one study suggesting superiority when compared with pamidronate (Lipton, 2002)(Vogel, 2004). Ibandronate, another bisphosphonate, is taken either orally or intravenously and has been shown in a small trial to reduce pain in women with metastatic breast cancer (Clemons, 2008). A newer compound, denosumab, is a monoclonal antibody that inhibits a receptor activator of nuclear factor kappa-B (RANK) ligand and reduces bone loss. It has

been approved for use in postmenopausal women at risk for osteoporosis (Cummings, 2009) and more recently in the prevention of skeletal events in patients with bone metastases due to solid tumors (Stopeck, 2010). Older agents, including clodronate and sodium etidronate, appear to provide little or no analgesia (Jagdev, 2001). A troubling adverse effect of bisphosphonates is the development of osteonecrosis of the jaw. This is more common when the drug is delivered intravenously, in those with cancer, and in patients who have had recent tooth extraction or dental surgery (King, 2008).

Topical Capsaicin: Topical capsaicin, believed to relieve pain by inhibiting the release of substance P has been shown to be useful in relieving pain associated with post-mastectomy syndrome, postherpetic neuralgia, and postsurgical neuropathic pain from cancer (Ellison, 1997). Discontinuation is common, however due to an increase in pain and burning. A high-concentration (8%) topical capsaicin patch applied for 1 hour has been shown to be effective in the relief of postherpetic neuralgia and human immunodeficiency virus-associated painful neuropathy (Backonja, 2008)(Simpson, 2008). This may one day be applied to cancerous neuropathic pain.

Radiopharmaceuticals: Radiotherapy, given as single or multiple fractions can be very effective in reducing pain associated with bone metastases or other lesions (Culleton, 2010). Painful and diffuse metastatic bone disease can also be well treated with radiolabeled agents in areas of high bone turnover . These agents deposit radiation directly to the affected region of the bone. The most commonly used and best studied radiopharmaceutical is strontium-89 (Gunawardana, 2004). Samarium-153 lexidronam, a radiopharmaceutical linked to a bisphosphonate compound has produced a positive clinical response (Sartor, 2004) and both strontium and samarium can reduce pain for 6 months or more in 60-80% of patients with metastatic breast and prostate cancers (Robinson 1993)(Sciuto 1996).

Opioid Therapy: Opioids are very effective analgesics, titrate easily, and offer a favorable risk/benefit ration. They reduce pain by binding to specific receptors located in the central and peripheral nervous system. Most of the commonly used opioids exert their effect through mu opioid receptors, though some bind to kappa or delta receptors. No compelling evidence supports the use of one opioid over another in managing cancer pain. The goal of minimizing adverse effects while maximizing analgesia remains paramount when selecting among opioids. Classification schemes include whether the opioid is a full agonist (morphine, oxycodone), partial agonist (buprenorphine), or mixed agonist-antagoinst (nalbuphine, pentazocine); whether the opioid provides short or long-term relief based on formulation (oxycodone versus sustained-release oxycodone); and where the opioid ranks on the federal schedule of controlled drugs (Table 6) according to their medical use and abuse potential This schedule includes drugs that are placed in Schedule I (high abuse potential and no medical use) to Schedule V (low abuse potential and accepted medical use). cost is another consideration when selecting opioids because high-cost agents can place undue burden on patients and families. Since there is no evidence that a specific opioid agonist is superior to another as first-line therapy, the agent that works for a particular patient is the "right" drug.

Prior to the discovery of opioid receptors in the central nervous system in 1973, only theories of their existence permeated the literature. Physicians inconsistently incorporated opioids into pain therapy for cancer patients and rarely in patients with non-cancer pain. Unfortunately, many cancer patients died in severe pain despite a developing scientific base and improvements in therapeutic approaches. New methods of drug delivery were introduced in the 1980s, such as intravenous, subcutaneous, epidural, and intrathecal infusions of opioids. The latter two techniques permitted more precise placement of opioids to their receptors and offered alternative means of analgesia.

(The following are listed alphabetically and not in any recommended order or precedence.)

Buprenorphine: Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa and delta receptors (Cowan 1977)(Lee 1999)(Lewis 2004). It has a high affinity for and slow dissociation from the mu receptor and may produce less analgesia than a full mu agonist.

Transdermal buprenorphine has recently been approved for use in the United States; it has been used in the management of cancer pain in Europe and trials have demonstrated this partial agonist is useful in relieving cancer pain (Muriel, 2005)(Sittl, 2003). Aside from its analgesic properties, buprenorphine is approved for the treatment of opioid dependence disorders in a combination product with naloxone (Gutstein, 2006). New data indicate that buprenorphine causes limited respiratory depression compared to fentanyl and probably other opioids (Dahan 2006). In fact, buprenoprhine may also have a ceiling effect for respiratory depression at high doses that is independent of its analgesic effect (Cowan 2003) and may have limited efficacy in palliative care. It is 25-50 times more potent than morphine, and is available in parenteral, sublingual, and transdermal formulations. A recent study of transdermal buprenorphine in cancer and noncancer patients showed that almost half of the patients reported satisfactory pain relief and over one-third experienced good pain relief (Likar 2006). Evidence from other studies demonstrates that buprenorphine provides improvement in pain, enhanced quality of life, and stable dosing in cancer pain patients (Pace 2007)(Sittl 2006)(Sorge 2004). Adverse effects, such as constipation and patch-related erythema and pruritis, appear at lower rates with buprenorphine than other opioids. For instance, constipation rates range from 0.97% to 6.7% in studies of transdermal buprenorphine (Greissinger 2005)(Likar 2005)(Sittl 2006). In contrast, transdermal fentanyl produces constipation at rates between 9% and 28% (Mystakidou 2003)(Nugent 2001). Buprenoprhine requires no dose adjustment in patients with renal failure, which confers a substantial advantage to vulnerable populations like cancer patients and older adults (Likar 2006). The liver metabolizes buperenorphine to norbuprenorphine, which represents its major, weakly active metabolite. This metabolite, along with others, passes into the bile and then into the feces which bypasses any accumulation in patients with renal dysfunction. The safe administration of buprenorphine in patients with renal imparment (Filitz, 2006)(Summerfield, 1985) offers a unique alternative to many other opioids that may accumulate and cause severe adverse events. The maximum recommended dose is 20 microgram/hour because, at greater doses, QT prolongation has been observed. This drug is located on step 3 of the WHO analgesic ladder for moderate-severe pain.

Codeine: Codeine is a relatively weak opioid that can be given alone, although it is more frequently administered in combination with acetaminophen. Codeine is a prodrug and must undergo liver glucuronidation to be converted to its active agents. This process is largely through the action of the liver enzyme CYP 2D6. The polymorphism seen in this enzyme varies between ethnic groups, and between individuals, and leads to a significant percentage of patients obtaining reduced analgesia (i.e. 3% Asian and African Americans and 10% of Caucasians are poor metabolizers) (Caraco, 1999)(Eichelbaum 1996). Accordingly, clinicians should consider rotating to other opioids in the event that certain patients fail to experience adequate relief from codeine. Interestingly, some individuals are ultrarapid metabolizers, leading to the possibility of increased serum levels and adverse effects (Kirchheiner, 2007)(Gasche, 2004). The WHO places codeine on step 2 of the analgesic ladder to be used for mild-moderate pain. Practitioners should avoid using codeine in patients with renal failure because its active metabolites accumulate (Guay, 1988) and can cause significant adverse effects (Matzke, 1986)(Talbott, 1997).

Fentanyl: Initially used as an intraoperative anesthetic, fentanyl's use has evolved into a popular transdermal, controlled systemic delivery formulation. The data support the effectiveness of transdermal fentanyl (fentanyl patch) for treating cancer pain (Ahmedzai, 1997)(Donner, 1998)(Radbruch, 2001) and most clinicians should place the drug on step 3 of the WHO analgesic ladder for moderate-severe pain. The fentanyl patch serves as a viable alternative to oral opioids, especially when cancer or adverse treatments effects preclude the oral administration of analgesics. Fentanyl is 100 times more potent than morphine (Gutstein, 2006) and is very lipid soluble, which affords easy passage of the drug through the skin and mucous membranes en route to systemic circulation. As an opioid for patient-controlled analgesia infusions of short duration, fentanyl has a relatively short time to peak analgesic effect and a quick termination of effect after small bolus doses; it provides marked cardiovascular stability (fentanyl releases no histamine) (Gutstein 2006). The transdermal system usually requires 12-24 hours before serum levels stabilize when starting the patch or changing the dose (Muijsers, 2001). Recommended dosing is every 72 hours, though some patients report an attenuated analgesic response by the 3rd day and request a shortened

dosing interval to every 48 hours. Many clinicians prescribe the patch to patients who display stable pain symptomatology due to the longer time needed to increase the dose to therapeutic levels (Hanks 2001). In addition to its transdermal formulation, fentanyl is administered intravenously, orally (lollipop, lozenge, buccal tablet), intraveneously, epidurally, and intrathecally. An innovative delivery system called the fentanyl iontophoretic transdermal system shows promise in treating postoperative pain (Hartrick, 2006)(Viscusi 2004) and may have future value in treating breakthrough pain among chronic cancer pain sufferers. This system represents a noninvasive, transdermal mehod of drug delivery in which an electrical field deposits small charged lipophilic particles to deeper tissues (Viscusi 2005). The liver and to a lesser extent the duodenum metabolize fentanyl to inactive metabolites. Based on limited data, clinicians can use fentanyl in patients with renal failure, but should monitor patients for evidence of gradual accumulation of the opioid (Dean, 2004).

Hydromorphone: Hydromorphone is introduced at step 3 of the WHO analgesic ladder for moderate-severe pain. It is a semisynthetic derivative of morphine that is about 7 times more potent. It binds to both the mu andto a lesser degree, the delta opioid receptors (Ananathan, 2004). Hydromorphone is available in oral (immediate-release and controlled release), parenteral (intravenous, intramuscular, subcutaneous), and intraspinal preparations. Randomized, controlled trials (RCTs) support the drug's efficacy and tolerability in patients with cancer pain and thus is included in clinical practice guidelines for the management of cancer pain (Junker, 2005)(Quigley, 2002)(WHO, 1990). Studies report that hydromorphone shares equivalency with morphine in analgesic efficacy and adverse effects (Quigley, 2002). Hydromorphone seems to have active, nonanalgesic metabolites (i.e. hydromorphone-3-glucuronide) which may lead to neuroexcitatory effects (myoclonus, allodynia, seizures, confusion) at high doses, prolonged use, or in the setting of renal dysfunction (Hagen, 1997)(Smith, 2000). Therefore, patients who present with increased pain, confusion, and myoclonus should rotate to another opioid or reduce the dose and frequency of administration. Since the metabolites are more readily dialyzable, it is a safer drug for those patients with renal failure who are undergoing dialysis (Niscola, 2010)

Methadone: Methadone is introduced at step 3 of the WHO analgesic ladder. It has several characteristics that make it useful in the management of severe cancer pain. Methadone is a long-acting opioid that is a mu and delta opioid receptor agonist and is an N-methyl-D-aspartate (NMDA) receptor antagonist, with affinity similar to ketamine (Bulka 2002)(Bernard, 2000)(Bulka 2002). This unique feature may make methadone a particularly useful choice for the treatment of neuropathic pain. The available data suggest that methadone is an effective analgesic in patients with cancer (Nicholson, 2004)(Grochow, 1989). Methadone also blocks the reuptake of serotonin and norepinephrine, another potentially favorable attribute in treating neuropathic pain. The prolonged analgesic half-life of methadone (ranging from 4-6- hours or more) allows for a dosing schedule every 8 hours (Davis, 2001). However, it displays complex and erratic pharmacokinetics requiring extreme vigilance in initiation and dose titration (Fainsinger 1993). Moreover, significant variability in plasma half-life between individuals has been observed in clinical practice (Ripamonti, 1997). Repeat administration in treating cancer pain, coupled with a prolonged half-life (plasma half life is approximately 24 hrs), increases the risk of oversedation and respiratory depression. This may occur after 2-5 days of treatment with methadone and therefore close monitoring of these potentially adverse or even life-threatening effects is required (Hanks, 2001)(Watanbe, 2002). Because of the variability in plasma half-life, the appropriate dosing ration between methadone and morphine or other opioids is not known. Infrequent (two to three times daily), low, and slow dosing along with vigilant monitoring can lend a margin of safety to clinicians when prescribing methadone. Caution is advised when rotating to methadone, especially from high doses of a previous opioid given its variable conversion ratio (Bryson 2006). Available formulations exist for oral, rectal, and parenteral administration. Patients taking monoamine oxidase inhibitors should not concurrently use methadone; additionally there are notable interactions with selective serotonin reuptake inhibitors (SSRI). Clinicians should be mindful of QT prolongation and the risk of torsades de pointes associated with higher doses of methadone (300mg and above), and methadone use in concert with certain antidepressants, severe hypokalemia or hypomagnesemia, and congestive heart failure (Reddy 2004)(Roden 2004). The liver transforms methadone to inactive metabolites (Kreek, 1976)

that are excreted in the urine and in the bile (feces). Since methadone seems to be metabolized through the CYP enzymes, drugs that inhibit CYP enzymes slow methadone metabolism, potentially leading to sedation and respiratory depression, whereas drugs that induce CYP enzymes accelerate the metabolism of methadone resulting in reduced serum levels of the drug, shortened analgesic periods, or reduced overall pain relief (Bernard, 2000). Renal dysfunction does not seem to impair clearance of the drug, so clinicians may consider methadone in patients with renal failure (Kreek 1980). Despite its hazards, methadone can serve as an ally in easing pain among gravely ill patients (Hanks 1998)(Twycross 1998). For example, methadone has high oral bioavailability (85%), has a long half-life, induces tolerance slowly, produces no active metabolites, and is much less expensive than comparable doses of commercially available continuous-release opioid formulations, hence, methadone can be a useful option for low income patients.

Morphine: Morphine remains the most commonly used opioid for treating severe cancer pain (step 3 of the WHO ladder). No other drug has demonstrated greater analgesic efficacy, though no controlled studies have proven morphine's superiority over other opioids. Although morphine was previously touted as the "gold standard," the most appropriate agent is the opioid that produces an optimal response in a particular patient. Morphine's wide availability, cost effectiveness, and multiple formulations (including oral, rectal, intravenous, intranasal, epidural, subcutaneous, intrathecal, and sustained-release) illustrate its preferred status for managing cancer pain. Oral administration is the preferred and simplest route. Morphine is metabolized in the liver, producing morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Although M3G is inactive, M6G is an active metabolite that exceeds morphine in potency and half-life. Both metabolites are excreted by the kidneys; however, patients with renal dysfunction may experience prolonged morphine effects, including respiratory depression from accumulation of M6G. Clinicians should consider small doses of immediate-release morphine and/or reducing the dosing frequency when prescribing morphine to patients with renal impairment. Some have advocated the avoidance of morphine altogether in patients with renal failure due to the risks of managing adverse effects of the metabolites (Dean, 2004)(Fitzgerald, 2001).

Oxycodone: Oxycodone may be useful as a step 2 or step 3 analgesic on the cancer pain ladder. It binds to both the mu (Monory, 1999)(Yoburn, 1995) and kappa (Prommer 2006) opioid receptors, and is often used in combination with acetaminophen as a short-acting analgesic. This synthetic opioid is primarily used orally in both immediate-release (capsule, liquid, tablet) and controlled-release forms to manage pain. Several RCTs document oxycodone's ability in controlled-release preparations to provide effective pain relief in moderate to severe cancer pain compared to sustained-release morphine (Bruera 1998)(Heiskanen 1997)(Mucci-LoRusso 1998). Further, patients in these studies reported fewer hallucinations with oxycodone as well as less pruritus and nausea compared to morphine (Heiskanen 1997)(Mucci-LoRusso 1998). Controlled release formulations of oxycodone and other opioids have greatly facilitated the provision of stable dosing and pain relief for patients with cancer pain. Controlled-release oxycodone, for example provides sustained relief for 12 hours and offers faster onset of relief than sustained-release morphine (Curtis 1999). In older adults, oxycodone may be a desireable alternative to morphine if patients are sensitive to morphine-induced sedation and mental status changes. The liver metabolizes oxycodone to oxymorphone and noroxycodone. Oxymorphone, an active metabolite can accumulate in patients with renal compromise, and thus requires physicians to be mindful of titration and dosage (Kirvela, 1996).

Oxymorphone: Oxymorphone, a semisynthetic opioid and metabolite of oxycodone is believed to be twice as potent as morphine (Sloan, 2005). It may reflect a new treatment option for cancer patients suffering from moderate-to-severe pain (step 3 on WHO analgesic ladder). Formerly available only as a parenteral or rectal agent, oxymorphone has recently been developed as immediate-release and sustained release (12-hour) formulations. Its analgesic effects are mediated through mu and delta opioid receptors (Ananathan 2004). In a pilot study, Sloan and colleagues found that oxymorphone produced equivalent analgesia to extended-release morphine or extended-release oxycodone in patients with moderate-to-severe cancer pain (Sloan, 2005). In fact, patients

taking sustained-release oxymorphone required less breakthough medication than those taking extended-release morphine. The half-life of the immediate-release formulation of oxymorphone (approximately 7-9 hours) (Adams 2005) exceeds that of many short acting formulations of opioids including morphine, oxycodone, and hydromorphone. Furthermore, the 6 hr recommended dosing interval is longer than the intervals for most immediate release opioids. Consequently, clinicians may find this an attractive option for limiting episodes of breakthrough pain. The liver biotransforms oxymorphone into oxymorphone 3-glucoronide and 6-hydroxyoxymorphone. Oxymorphone is renally excreted and accumulates in renal failure, so clinicians should be mindful about prescribing this in the setting of renal dysfunction.

Tapentadol: Tapentadol is a new opioid that binds to the mu opioid receptor and inhibits norepinephrine reuptake. It is noteworthy that clinical trials suggeest fewer gastrointestinal (GI) adverse effects when compared to oxycodone. Further research is needed to determine its utility in cancer pain (Wade, 2009)(Prommer, 2010).

Tramadol: Tramadol is a centrally acting analgesic that shares properties of both opioids and TCAs. Technically, it is a synthetic oral opioid that binds to the mu opioid receptor and blocks reuptake of serotonin and norepinephrine, and promotes neuronal serotonin release. The WHO places tramadol on step 2 of the ladder as an option for treating mild to moderate cancer pain. It is often used for its opioid-like analgesic effects in the cancer population, although it may be incorporated into the armamentarium of drugs considered for neuropathic pain. For instance, a recent RCT of tramadol compared to placebo demonstrated efficacy in controlling neuropathic pain in patients with cancer (Arbaiza, 2007). Furthermore, high quality studies in patients with nonmalignant neuropathic pain (Boureau 2003)(Harati 1998) confirm its efficacy in treating this painful condition. Clinicians feel comfortable using tramadol because it is not listed on the federal schedule of controlled drugs, has low abuse liability (Macaluso, 1988), and is associated with low risk of respiratory depression (Shipton, 2000). Adverse effects resemble those of opioids and caution is advised when using tramadol with SSRIs, monoamine oxidase inhibitors, or TCAs given the potential for serotonin syndrome. Tramadol is available in immediate-release form or in combination with acetaminophen, and now in a controlled-release preparation (Babul, 2004). Use tramadol cautiously in patients with a history of seizures. Tramadol is thought to be approximately one-tenth as potent as morphine in cancer patients (Grond, 2004); therefore, the ceiling dose is generally considered to be 400mg/day. Tramadol may produce adverse effects which include vomiting, dizziness, weakness when compared to hydrocodone and codeine in a double-blind study of cancer patients (Rodriguez, 2007).

Meperidine: The opioid binds predominantly to the mu opioid receptor and is used most often as an intraoperative analgesic. Small, single doses are effective for postoperative shivering as well. The drug may produce an anticholinergic response in the form of tachycardia and acts as a weak local anesthetic. Oral and parenteral formulations are available for clinical use. Most clinicians avoid meperidine for the treatment of chronic pain and cancer pain due to its short duration of action and concerns over metabolic toxicity. In fact, the Agency for Health Care Policy and research recommends its use for no longer than 48 hours and in doses that do not exceed 600mg per day (Acute Pain Mgmt, 1992). Hence, this drug is rarely recommended as a therapeutic agent listed on the WHO analgesic ladder. Meperidine is metabolized to normeperidine which is eliminated by both the liver and the kidney; therefore, hepatic or renal dysfunction can lead to metabolite accumulation. Normeperidine toxicity manifests as shakiness, muscle twitches, myoclonus, dilated pupils, and seizures (Hershey, 1983). Renal failure greatly elevates the risk of normeperidine neurotoxicity, therefore clinicians should avoid its use in patients with kidney disease. Furthermore, co-administering monoamine oxidase inhibitors with meperidine can yield serious reactions, such as delusions, hyperpyrexia, respiratory depression or excitation, and convulsions. For this primary reason, like meperidine propoxyphene, is not recommended in cancer pain management due to the neurotoxic effects of norpropoxyphene (Kaiko, 1983).

Butorphanol: Butorphanol is a mixed agonist-antagonist opioid analgesic. Other drugs in the same class include nalbuphine and pentazocine. None of these medications are recommended in cancer pain management due to their analgesic ceiling effect. Thus, uptitration of these drugs is more likely to cause psychotomimetic effects rather than improve analgesia. Moreover, as cancer patients require escalating doses of opioids, use of these agents may precipitate abstinence syndrome if given to a patient that has become physically dependent on a pure opioid agonist.

The "4ᵗʰ Step" Interventional Procedure: Some have added a fourth step in the WHO analgesic ladder to consider procedural interventions. For instance, celiac plexus block/neurolysis for visceral pain in the upper abdominal quadrants secondary to pancreatic cancer.We will not discuss this interventional step herein, however it is important to note that an array of interventional procedures may be appropriate for the cancer patient if attempts to control pain with medication management fail. These interventions are not without their own risks and benefits; therefore, discussion amongst a multispecialty pain team may allow for the full breadth of care a cancer pain patient may need.

Conclusion: Cancer pain remains difficult to treat despite the wide array of interventions and medications availableAlthough the WHO cancer pain analgesic ladder and pain assessment tools help direct pain management, it is becoming increasingly apparent that a multidisciplinary team approach with equal involvement of the patient is essential for comprehensive care of the patient's pain. Furthermore, concerns about opioid compliance, diversion, abuse, and addiction all prevent the proper and therapeutic use of opioids in relieving cancer pain. . The available evidence suggests that rates of problematic opioid use in this population are low; therefore, patients should not be denied opioid therapy for fear of inducing stubstance abuse. Clinicians should consider the range of medical therapies (primary, adjuvant, nonopioid, and opioid) available for patients suffering from cancer pain, and incorporate them into a treatment strategy that maximizes analgesia and minimizes adverse effects. Finally, physicians should be aware of a fourth step in the WHO analgesic ladder that offers interventional therapies such as celiac plexus neurolysis if medication management fails. Uncontrolled pain is incompatible with a satisfactory quality of existence, and multiple studies highlight the deleterious impact of persistent pain on daily life and social interaction. Accordingly, all practitioners must make control of cancer pain a professional duty, even if they can use only the most basic and least expensive analgesic medications such as morphine, codeine, and acetaminophen to reduce human suffering.

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