Cancer Pain Management Circa 1986

Two decades ago, basic information on the biology of pain was changing rapidly. The original theory proposed by Rene Descartes in 1664 described pain as a reflex that traveled through a single channel to the brain. This was challenged by the gate-control theory postulated by Melzack and Wall in 1965.[1] This novel framework conceived of pain as a dynamic and interlocking series of biologic mechanisms, prompting research on central sensitization and central nervous system plasticity.[2] Opioid receptors were discovered in the late 1970s, suggesting that endogenous opioids existed and that these acted centrally in the nervous system. Further studies described activation and sensitization of nociceptors and mechanoreceptors, effects of endogenous agents (epinephrine, serotonin, bradykinin, and prostaglandins), deafferentation pain states, and alterations in the autonomic nervous system with sensitization of perivascular receptors.

Advances in Drug Therapy

In the 1980s, the available opioid agonists included morphine, meperidine, methadone, levorphanol, oxycodone, heroin, hydromorphone, oxymorphone, and codeine as well as the mixed agonist-antagonists pentazocine, nalbuphine, butorphanol, and buprenorphine. Adjuvant agents, such as phenytoin, carbamazepine, and tricyclic antidepressants for neuropathic pain, corticosteroids for epidural cord compressions, nonsteroidal anti-inflammatory agents, and cocaine (Brompton's cocktail) were prescribed for severe pain. In addition, novel methods of drug administration were being studied. These included continuous intravenous and subcutaneous infusions of opioids as well as continuous epidural and intrathecal morphine infusions, which placed opioids adjacent to the recently described opioid receptors. In addition, anesthetic approaches (trigger point injections, blocks of peripheral and autonomic nerves), epidural and intrathecal local anesthetics, neurolytic blocks, and neurosurgical approaches (dorsal rhizotomy, dorsal root entry zone lesions, cordotomy of midline myelotomy, and placement of neurostimulators) had been described. Also, computed tomographic (CT) scans became available, allowing clinicians to better visualize lesions causing pain.[2,3]

Need for Education and Drug Access

Despite the expanding scientific base, more accurate diagnostic tools, and a broad range of available therapeutic approaches, however, a high percentage of patients with cancer in the 1980s were dying with severe pain. Medical students and house staff were not trained in the evaluation of treatment of
cancer pain, and there were no institutional guidelines to ensure that pain was appropriately assessed or treated. In developing nations, these problems were compounded by a lack of opioid availability.

In 1986, the World Health Organization (WHO) published a monograph titled *Cancer Pain Relief* in an attempt to promote education and opioid availability. The principles of cancer pain management were simplified using the "three-step analgesic ladder" (Figure 1).[4] This suggested that physicians begin therapy with aspirin or acetaminophen and then escalate to codeine and, if necessary, to morphine. Other key concepts in this monograph included using oral medications whenever possible, dosing around the clock rather than waiting for severe pain, and making modifications to each patient's regimen to maximize relief.

![Figure 1: WHO Cancer Pain Ladder](image)

Although innovative at its inception, the three-step analgesic ladder has subsequently been criticized as being too simplistic and not including interventional modalities to cancer pain management. At the time, however, it fulfilled the global need to promote an uncomplicated therapeutic approach and to emphasize the use of an individual patient's pain rating to adjust medications. The WHO also maintained that all cancer programs should provide pain and palliative care services.

**Cancer Pain Management Circa 2006**

There have been no dramatic breakthroughs during the past 2 decades that have solved the cancer
pain problem. Instead, incremental progress in basic science, technology, and the routine application of diagnostic and therapeutic algorithms have increasingly permitted clinicians to provide more effective therapies to patients with cancer pain. Further scientific advances have elucidated additional components of the intricate mechanisms and modulation of pain.

The pain process is now thought to occur on at least three levels—peripheral, spinal, and supraspinal. At the periphery, pain impulses are transmitted via the myelinated A fibers or the unmyelinated C fibers. These fibers synapse in the dorsal horn of the spinal cord. The gate-control theory holds that signals from the periphery increase or decrease the flow of impulses to the higher central nervous system. Ascending pathways carry signals to the higher modulatory centers, and descending inhibitory pathways inhibit the release of substance P from the dorsal horn. This occurs indirectly by the release of endogenous opioids, a finding that led to the concept that the descending inhibitory pathways serve as the primary endogenous system for pain control.

Many neurotransmitters are being investigated for their role in pain transmission. For example, researchers are exploring the function of gamma-aminobutyric acid, adenosine, glycine, calcitonin gene-related peptide, and glutamate. Pain control strategies have focused on specific targets within this complex, integrated matrix by blocking pain at the periphery (nonsteroidal anti-inflammatory agents, regional anesthesia), by activating inhibitory processes at the spinal cord and brain (opioids, clonidine, tricyclic antidepressants), and by interfering with the perception of pain (complementary medicine, hypnosis, relaxation techniques, biofeedback).

In addition, pain is now thought to be an active process with changes in the nervous system occurring as a direct response to stimuli. Woolf and Salter referred to this as neuronal plasticity in 2000. This process results in exaggerated pain sensitivity, hypersensitivity, chronic inflammation, and neuropathic pain. These concepts have led to an emphasis in treating cancer pain effectively in order to prevent lasting changes to both the peripheral and central nervous system components.

**Therapeutic Approaches**

**Opioids**

No unique opioids have emerged during the past 20 years. Morphine remains the opioid of choice for the treatment of cancer pain even though there are no controlled trials to prove its superiority over other opioids. The agent is widely available, inexpensive, used via oral, rectal, intravenous, subcutaneous, epidural, and intrathecal administration, and the doses and pharmacology are familiar to most physicians. Hydromorphone, like morphine, acts at the mu and delta receptors and can be administered orally, parenterally, and intraspinally. It is about six times more potent than morphine, which makes it an attractive opioid for subcutaneous infusions.

Oxycodone is limited to the oral route and has been the subject of considerable attention regarding drug diversion. Oxymorphone, the active metabolite of oxycodone, is available as a rectal suppository (Numorphan) and has recently been approved for extended-release oral use (Opana). Fentanyl is a short-acting agent that is widely prescribed in a transdermal patch, which lasts for 48 to 72 hours. It is also administered intravenously as a short-acting opioid by bolus injection, as a continuous intravenous infusion, in an oral transmucosal delivery system (Actiq), or as a buccal tablet (Fentora) for breakthrough pain. Methadone is an inexpensive oral opioid with a long pharmacologic half-life. Historically used perioperatively, meperidine should be avoided, given its lack of potency and numerous toxicities, including neuroexcitatory effects.

Not a controlled substance, tramadol is an atypical mu receptor and norepinephrine agent that is frequently utilized for its opioid-like effects. However, the drug must be used with caution due to numerous associated drug-drug interactions. Long available in regular-release form and combined with acetaminophen, tramadol is also now available in an extended-release tablet (Ultram ER).

**Advances in Opioid Delivery**

Although the available opioids have remained relatively constant during the past 2 decades, technologic advances have dramatically changed how these agents are used in patients with cancer (Table 1). Most of these agents have a short half-life requiring that they be administered every 3 to 4 hours. Since the 1980s, a variety of sustained-release oral opioid formulations have been developed.
Morphine and oxycodone are currently marketed in oral formulations that allow them to be administered every 8 to 24 hours, thereby improving compliance and resulting in fewer fluctuations of opioid levels during the day. A sustained-release oral hydromorphone product was briefly on the market in 2005, and sustained-release oral oxymorphone is now available. The US Food and Drug Administration (FDA) recently approved a sustained-release morphine formulation (DepoDur) designed for epidural administration in the postoperative setting. The otherwise water-soluble morphine is encapsulated in a liposomal preparation, designed for epidural analgesia for 48 hours without a catheter or patient-controlled analgesia (PCA) pump. Recently introduced and designed predominantly for acute pain, intranasal morphine allows for rapid absorption through the nasal mucosa.[11]

Fentanyl, a very lipid-soluble opioid, is able to pass through skin and mucous membranes to gain access to the systemic circulation. The transdermal patch was initially evaluated in postoperative pain, but it can cause serious respiratory depression in opioid-naive patients. As a result, it is now primarily administered to opioid-tolerant patients with relatively constant levels of pain.[12] An iontophoretic (ion-mediated, active cellular transfer) transdermal patient-controlled analgesia device will soon be available for postoperative pain. A fentanyl effervescent buccal tablet for rapid absorption into the oral mucosa was just approved by the FDA.

In addition to products that provide a slow continuous release of opioids when administered by oral, epidural, and transdermal routes, the development of external and implantable pumps has dramatically changed the care of patients with cancer pain. These computerized pumps can deliver a specified continuous-infusion rate with or without patient-controlled bolus doses, specify a lockout time, record exactly how much opioid has been administered, and document the historical number of successful and unsuccessful bolus attempts. Studies have demonstrated that patients achieve better pain control with less opioid when they control their rescue dosing. These PCA pumps are now routinely used in cancer centers for intravenous, subcutaneous, and intraspinal opioid infusions, rapid dose titrations, and difficult-to-Manage breakthrough pain.[13]

Improvements in Opioid Prescribing
Clinicians and investigators have learned valuable lessons in administering opioids during the past 20 years. Examples of these include the need for appropriate opioid conversions, the use of opioids in patients with renal and liver dysfunction, special issues in methadone and fentanyl prescribing, and the appropriate treatment of opioid toxicities.

- **Opioid Conversions**—Opioids have distinctly different potencies based on the drug and the route
of administration. A common error in the management of these patients is to change the drug and/or the route without appropriately calculating the parenteral opioid equivalents between the old and the new opioid regimen. Although, this can be done by using opioid equivalency tables found in textbooks, software is available for handheld organizers using the Palm or Windows operating systems (www.hopkinsopioidprogram.org), or for Web-based applications (www.hopweb.org). Many of these resources are free of charge, providing opioid conversions, cautions regarding prescribing, available formulations, and important references.

- **Methadone**—Methadone is a potentially difficult drug to use in patients with cancer pain. Its pharmacologic half-life (> 24 hours) is considerably longer than its analgesic half-life (4-6 hours).[14] As a result, drug continues to accumulate for approximately 5 days after changing doses, with the ongoing possibility of delayed respiratory depression. Moreover, recent data suggest that equianalgesic conversion ratios with methadone are not linear in patients taking large amounts of opioids, thereby underestimating the potency of methadone in opioid-tolerant patients.[15] This can result in serious underdosing or overdosing when converting to or from another opioid.[16,17] In addition, methadone interacts with other agents that may be used in patients undergoing cancer therapy.

- **Fentanyl**—The transdermal fentanyl patch was introduced to the market in 1990. Pharmacologic studies demonstrate that it may take 72 hours after placement of a transdermal patch to reach peak fentanyl levels in the serum. As a result, titrations are necessarily slow. Similarly, when a transdermal patch is removed, it will take approximately 72 hours before systemic fentanyl levels have fallen to zero. Fatal respiratory depression has been described when this delivery system is prescribed to opioid-naive patients.[18] Equianalgesic conversion ratios for the transdermal delivery systems have not been well defined. In addition, this method of opioid administration is best suited to patients with relatively stable, rather than fluctuating, levels of pain.[19] The transmucosal fentanyl product used for breakthrough pain is expensive. Clinical studies have shown that the effective dose of transmucosal fentanyl is not related to the daily dose of opioids that patients are taking. As a result, titration of the transmucosal fentanyl is required to determine whether this is an effective product for the patient.[20]
**Renal Dysfunction**—The active metabolites of morphine, hydromorphone, and meperidine have been shown to accumulate in the serum of patients with renal dysfunction. This can result in severe neurologic side effects including seizures and potentially life-threatening overdoses.[21] As a result, it is recommended that fentanyl, oxycodone, or methadone be used in patients with severe renal dysfunction.

**Opioid Side Effects**—Progress has also been made in the treatment of common opioid side effects including sedation, constipation, pruritus, nausea, and vomiting. Many patients adjust to sedation with time. Stimulants, modafinil (Provigil), laxatives, and newer antiemetics make a significant difference in selected patients. As some patients tolerate one opioid better than another, switching to another opioid may reduce side effects. Opioid rotation can also be considered if a patient becomes tolerant to one opioid. If opioids are effectively controlling pain but intolerable side effects persist, intraspinal opioids can be considered, as these offer analgesia while reducing systemic exposure to the drug.

**Nonopioid Advances**

**Neuropathic and Bone Pain**—Over the past 2 decades, novel agents have become available for the treatment of neuropathic and bone pain. In the 1980s, the basic options in this setting were tricyclic antidepressants and antiepileptics. In recent years, however, serotonin and dual serotonin-norepinephrine-reuptake inhibitors have been shown to produce substantial effects in attenuating neuropathic pain. Newer anticonvulsants such as gabapentin and pregabalin (Lyrica) are frequently helpful for neuropathic pain.[22] These agents target excitatory (glutamate) and inhibitory (GABA) neurotransmitters, inhibiting membrane sodium channels and voltage-gated calcium channels.[23] Ziconotide (Prialt), a potent blocker of N-type voltage-sensitive calcium channels, was recently approved for patients with neuropathic pain. This synthetic analog of a toxin found in a marine snail is administered intrathecally.[24,25] In addition, topical agents that inhibit local nociceptive pathways, such as capsaicin cream, lidocaine, or clonidine patches (Catapres-TTS), and transcutaneous electrical nerve stimulation (TENS) have expanded the therapeutic options for patients with neuropathic pain.

The incidence of symptomatic bone metastases continues to rise as the survival of patients with cancer continues to improve. For patients with isolated symptomatic bone metastases, local treatments are often employed, including external-beam radiotherapy, radiofrequency ablation, or modern surgical techniques to replace joints or stabilize long bones or vertebral bodies.[26,27] In patients with diffuse bone metastases, radioisotopes such as strontium-89 and sumarium-153 may be indicated. These localize primarily to areas of osteoblastic metastases but can be associated with considerable myelosuppression. Bisphosphonates, which inhibit osteoclastic bone resorption, significantly reduce skeletal events in patients with bone metastases.[28,29]

**Imaging, Surgery, and Radiation**—General advances in medical imaging, surgery, and radiation over the past 20 years have been very helpful to patients with cancer pain. Understanding the etiology of the pain is critical to being able to treat it effectively. Standard x-rays and tomograms have been replaced by high-resolution computed tomographic and magnetic resonance imaging that allows clinicians to identify the location and dimensions of lesions causing pain. These imaging advances also allow for image-guided procedures, including focal anesthesia, catheter insertion to relieve painful obstructions, injection of stabilizing agents into collapsed vertebral bodies, and drainage of symptomatic fluid collections.

Surgical advances in the treatment of pathologic fractures or impending fractures keep cancer patients ambulatory and in much less pain than in the past. Secondary to surgical advances, recent studies have documented that carefully selected patients with advanced epidural cord compressions have less pain and better neurologic function when treated by surgery followed by radiation rather than radiation therapy alone.[30] Improvements in radiation therapy techniques now allow highly focused and carefully contoured beams, which target the tumor and miss nearby critical structures.[27]

**Changes in the Health-Care Environment**

Despite the scientific, pharmacologic, and technologic advances relating to pain management, unrelieved pain remains a major medical problem. In 1986, the World Health Organization published the Cancer Pain Relief monograph promoting the three-step analgesic ladder (Figure 1). The overly simplistic WHO three-step analgesic ladder was based on the premise that most patients should have adequate pain relief if health-care providers learned to use a few effective drugs and administered them regularly, according to each patient's needs.[31] This monograph has served as a powerful educational tool and has been widely cited. However, a paucity of controlled clinical trials have been conducted to document the effectiveness of this approach.[32]
As a result, the American Pain Society, the National Comprehensive Cancer Network, and other professional organizations have drafted more comprehensive clinical practice algorithms.[33-35] These excellent documents contain virtually all that is needed for a house staff, primary care physician, or specialist to make informed decisions regarding the evaluation and management of cancer pain (Figure 2).[36] They include detailed descriptions of a pain assessment and specific pain syndromes, principles of dose titration, proper use of short- and long-acting products, the management of opioid side effects, the role of coanalgesics and subspecialty consultations, and the critical aspects of patient and family education and psychosocial support.

In 2001, recognizing the widespread undertreatment of pain, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) launched new standards for assessing and managing pain that require organizations to meet rigorous standards in order to fulfill the requirements for reaccreditation (Table 2).[37] This effort has served to emphasize the importance of assessing and treating pain in inpatient and outpatient settings. In addition, palliative care and hospice programs have proliferated in the United States. Training programs have emerged, validated measurement tools are available to quantify pain, and the clinical research methods used to document efficacy of a novel drug or procedure have changed dramatically since the 1980s.
Unfortunately, despite the scientific, therapeutic, and health-care advances of the past 20 years, barriers to providing adequate pain management to patients with cancer persist (Table 3),[37] and current estimates suggest that as many as 50% of patients are inadequately treated.[38]
In 2006, the major challenge in controlling pain in patients with cancer is a practical one. We clearly have the appropriate diagnostic and therapeutic tools as well as the knowledge and societal resources required to ensure that the vast majority of patients with cancer pain can be comfortable during their illness. Yet barriers to appropriate pain management have persisted for decades (Table 1) and cancer pain remains undertreated in inpatient and outpatient settings.[39] This is not an American or a Western issue but one that confronts developed and developing nations around the world. The problem is highlighted by the continued lack of available morphine in most countries over the past 20 years. Figure 3 provides the annual per capita consumption of morphine in 2004 by country. Most morphine used in nations with a limited supply is administered parenterally to postoperative patients for a very limited time rather than to patients with cancer. Poorer nations have limited funds to spend on pharmaceutical agents. Often these limited resources are allocated for vaccines, antibiotics, and treatable illnesses in individuals with favorable prognoses.[40] In addition, opioids raise concerns about compliance, the storage of medications in crowded dwellings, drug diversion, and associations with drug abuse, violence, and AIDS. As a result, these effective and inexpensive medications for patients with cancer pain remain low on national priority lists. Perhaps the most sobering aspect of this global view is that cancer pain remains undertreated even in the United States, where there is a relative abundance of opioids, health-care providers, and health-care resources. This suggests that the primary way to resolve this practical challenge worldwide is to make alleviating pain a major health-care priority. An effective strategy to achieve this important goal remains to be defined.

References:


**Links:**