WHAT EVERY PROFESSIONAL WORKING IN PALLIATIVE CARE SHOULD KNOW ABOUT CANCER PAIN MANAGEMENT

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Resumen

El cuidado paliativo y el manejo del dolor están profundamente unidos en la práctica diaria. La actualización de los conocimientos fundamentales acerca del estado actual de los conceptos y técnicas para el manejo de los pacientes con Cáncer es de una enorme importancia para todos los profesionales que manejan este tipo de pacientes, tanto como fuente de información como de soluciones a sus problemas. El dolor agudo y crónico ocurre con gran frecuencia en los pacientes con cáncer, por lo cual la evaluación y el tratamiento inadecuados puede interferir con el tratamiento antitumoral y deteriorar su calidad de vida. Mientras que el control del dolor es importante independiente del estado de la enfermedad, se convierte en una prioridad en pacientes con estados avanzados de la enfermedad y que no son candidatos para terapias potencialmente curativas bajo el espectro de un cuidado paliativo integral.

Palabras clave: dolor, cáncer, evaluación del dolor, tratamiento del dolor en cáncer, cuidados paliativos.

Abstract

Palliative care and pain management are closely bounded to everyday practice.

A basic knowledge update about the current status of concepts and techniques for Cancer pain management is of enormous importance for every pactioner caring for Cancer patients as a resource for appropiate information and solution to their pain problems. Acute and chronic pain occurs in a high frequency in Cancer patients. Inadequate assessment and treatment of pain and other distressing symptoms may interfere with primary antitumor therapy and markedly detract from their quality of life . While a strong focus on pain control is important independent of disease stage, it is a special priority in patients with advanced disease who are no longer candidates for potentially curative therapy under the scope of an integral perspective to palliative care.

Key word: pain, cancer, pain assessment, pain cancer treatment, palliative care.

INTRODUCTION

From all dimensions and symptoms that makes difficult to live with cancer, Pain is probably the most unpleasant and detrimental symptom for the quality of life. Whether it is in the active or palliative treatment phase, or if the patient is a Cancer survivor, no single achievement in the re-structured life of these patients after their diagnosis is made can be enjoyable if uncontrolled Pain is present.

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The pourpose of this paper is to present a wide scope of our current view of the general context, ethiology, mechanisms, and the treatment approaches from the basis to the most refined and updated interventions in order to control cancer pain. Its relation to decision-making in palliative care is remarked when feasible, and the final target is to serve as a reference paper for the non-pain specialist in a daily multidimensional practice towards quality of life improvement in patients remarkably associated with severe pain.

Cancer pain is defined as pain that is attributable to cancer or its therapies[1]. The more general and accepted definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue dam-

age, or described in terms of such damage"[2] relates better to Palliative Care, on which daily practice every symptom is deeply influenced by the context, the expectations and all type of emotional experiences of the cancer patient. Cancer pain is a problem that has attained a rising level of recognition among the health care community. Optimal management involves careful assessment, optimal analgesia, intensive follow-up and a proactive approach to treatment. Adequate control of pain can be achieved in the majority of patients with a rigorous and aggressive application of a treatment algorithm that is ultimately quite straightforward[3, 4]. Control of pain and related symptoms promotes an enhanced quality of life, improved functioning, better compliance and a means for patients to focus on those things that give meaning to life[5]. In addition to their salutary effects on quality of life, mounting evidence suggests that good pain control influences survival[6,7].

Approximately 6.35 million new cases of cancer are diagnosed worldwide annually, half of which originate in developing nations[8]. The WHO estimates that by the year 2021, there will be 15 million new cases of cancer worldwide annually. This will lead to cancer patients living longer with pain due to cancer disease itself and with therapy, which brings the need for a better symptom control in extreme situations both for pain and for other symptoms in Palliative Care. Approximately 1.04 million new diagnosis of cancer are made annually in the United State alone[9]. One of every five death in the United States is a result of cancer, which is approximately 1400 cancer related death daily[10]. The incidence of cancer increases with age and is particularly problematic given our rapidly aging population. It is estimated that up to 50% of patients undergoing treatment for cancer and up to 90% of patients with advanced cancer have pain[11]. Most (70%) cancer pain is due to tumor involvement of organic structures, notably bone, neural tissue, viscera, or others. Up to 25% of cancer pain is due to therapy, including chemotherapy, radiotherapy, or surgery. Up to 10% of "cancer pain" is accounted for by common chronic pain syndromes, including back pain and headaches, which might have been exacerbated by the ongoing growth or treatment of cancer[12].

Overall, cancer cure rates have not changed markedly over the past 4 decades: the overall 5-year survival rate for patients diagnosed with cancer in United States is still only about 40 to 50 %[13] and as a result of inadequate early detection, is less than one third worldwide[8]. The annual mortality rate is about 4.3 million worldwide and about 510,000 in the United States[9]. Palliative treatment, which may extend survival, is often more successful than therapies with curative intent, and as a result, there is an increasing number of patients to bearing advanced disease with associated chronic pain. Furthermore, the last decades advances in cancer treatment has increased not only the life expectancy but the number of survivors of a once fully mortal disease, increasing also the number of patients residual pain from cancer treatment that needs palliative treatment.

CANCER PAIN STATISTICS

Together with anorexia and fatigue, pain is among the most common symptom associated with cancer[14,15]. Significant pain is present in up to 25% of patients in active treatment and in up to 90% of patients with advanced cancer[11, 16 -20]. According to several studies including a survey of oncologists in the Eastern Cooperative Oncology Group (ECOG) and a survey of 1103 consecutive admission to a U.S tertiary care cancer hospital, 73% of patients in active treatment admitted to pain with 38 % reporting severe pain[21]. Despite the availability of simple, cost-effective treatment[22], inadequately controlled pain remains a significant problem.

Studies following the WHO cancer pain ladder (e.g. oral analgesics and careful follow-up) have achieved favorable outcomes in the 70 to 90 % range[23] suggesting that the key to achieving more effective global cancer pain relief involves applying known technology more effectively rather than development of new medical technologies or drugs.

While a variety of such factors have been identified, authorities agree that so-called "opiophobia", a reluctance to use opioids, largely because of exaggerated concerns of addiction and regulatory reprisal, exerts a potent influence at all levels and probably is the single most important impediment to better symptom control globally. In general, in Western developed sectors, barriers are largely educational and attitudinal in nature, while in developed nations a multitude of resource and access problems are operant. As an example, negative indirect effects on survival may stem from the negative influence of pain on performance status. When performance status is low, as is often the case when pain is severe, patients may find it difficult to tolerate recommended chemotherapy, indeed they may not be considered candidates for chemotherapy. Further benefits of good pain management often include improvements in nutrition, rest and mood, all of which contribute to quality of life and have the potential to influence the outcome of antineoplastic therapy.

EVALUATION AND ASSESSMENT

Pain is always subjective and is experienced only by the patient. Over the past 20 years, the assessment of pain has been the subject of much research and refinement of techniques and instruments, from which the most relevant are described below:

Many pain clinics utilize a questionnaire to aid in and standardize assessment. The Wisconsin Brief Pain Inventory (BPI)[24,25] and Memorial pain assessment card[26] are well accepted and standard tools for assessing cancer pain. At The University of Texas MD Anderson Cancer Center, an institutionally approved MD Anderson questionnaire (modified BPI) is used for initial and follow-up assessment of patients.

Numerous tools are available for assessing cancer related pain including:

1. Wisconsin Brief Pain Inventory:

a. 15-minute questionnaire, which can be self-administered.

b. Includes several questions about the characteristics of pain, including its origin and their effects of prior treatments.

c. It incorporates two valuable features of the McGill Pain Questionnaire, a graphic representation of the location of pain and groups of qualitative descriptors. Severity of pain is assessed by a series of VAS that score pain at its best, worst and on average. The perceived level of interference with normal function is quantified with VAS also.

Preliminary evidence suggests that the BPI is cross-culturally valid[24,25] and is useful, particularly when patients are not fit to complete a more through or comprehensive questionnaire.

2. Memorial Pain Assessment Card:

a. It is a simple efficient, and valid instrument that provides rapid clinical evaluation of the major aspects of pain experienced by cancer patients[26].

b. It is easy to understand and use and can be completed by experience patients in 20 seconds.

c. It consists of two-sided 8.5x11 inch card that is folded so that four separate measures are created.

d. It features scales, intended for the measurements of pain intensity, pain relief, mood and a set of descriptive adjectives.

3. Edmonton Staging System:

a. It is performed by health care providers

b. It was developed to predict the likelihood of achieving effective relief of pain in cancer patients[27,28].

c. The system's originators have provided validation that treatment outcome can be accurately predicted according to five clinical features (Neuropathic pain, movement-related pain, recent history of tolerance to opioids,

psychological distress, and a history of alcoholism or drug abuse).

d. Staging requires only 5-10 minutes and requires no special skills.

e. Its value lies in prospective identification of potentially problematic patients, further legitimizing clinical research on symptom control by introducing better standardization and improving our ability to assess critically the results of various therapeutic interventions in large population of patients.

4. Pediatric Cancer Pain Assessment:

This includes Beyer's The Oucher, Eland's color scale-body outline, Hester's poker chip tool, McGrath's faces scale, and others[29-32].

5. Numerical Pain Rating Scale (NRS) or Visual Analog Scale (VAS):

Pain is assessed on an 11 point numerical rating scale from 0 (no pain) to 10 (worst pain imaginable). The VAS is a 10 cm line without markings from no pain to worst pain; the patient marks their pain score and a measurement in cm defines their level of pain.

Objective observations of grimacing, limping, and vital signs (tachycardia) may be useful in assessing the patient, but these signs are often absent in patients with chronic cancer pain. Pain evaluation should be integrated with a detailed oncological, medical, and psychological assessment. The initial evaluation should include evaluation of person, his or her feelings and attitudes about the pain and disease, family concerns and the patient's pre-morbid psychological history. A comprehensive but objective approach to assessment generates confidence in the patients and family that will be valuable throughout treatment.

A **comprehensive evaluation** of the patients with cancer pain includes the following:

1. The chief complaint is obtained to ensure appropriate categorization or triage (e.g. severe pain with a bowel obstruction may need to be sent to the emergency center for urgent treatment).

2. Next, the oncologic history is obtained to gain the context of the pain problem. The oncologic history includes: diagnosis and stage of disease, therapy and outcome-including side effects, and the patient's understanding of the disease process and prognosis.

3. The pain history should include any premorbid chronic pain and for each new pain site must include: Onset and evolution, site and radiation, pattern (constant, intermittent, or unpredictable), intensity (best, worst, average, current) 0-10 scales, quality, exacerbating and relieving factors, pain interference with usual activities, neurological and motor abnormalities (including bowel and bladder continence), vasomotor changes, current and past analgesics (use, efficacy, side effects). Prior analgesic use, efficacy, and side effects should be cataloged. Prior treatments for pain should be noted (radiotherapy, nerve blocks, physiotherapy, etc.)

4. Review of medical record and radiological studies: Many of the treatments for cancer can cause pain themselves (chemotherapy, and radiotherapy induced neuropathies or postoperative pain syndromes; post-thoracotomy pain syndromes and post-mastectomy pain syndrome), and many specific cancers can cause well established pain patterns due to known likely sites of methastasis as: a) Breast to long bones, spine, chest wall, brachial plexus, and spinal cord, b) Colon to pelvis, hips, lumbar plexus, sacral plexus and spinal cord, c) Prostate to long bones, pelvis, hips, lung and spinal cord.

5. Psychological History: This should include marital and residential status, employment history and status, educational background, functional status, activities of daily living, recreational activities, support systems, health and capabilities of spouse or significant other, past history of (or current) drug or alcohol abuse.

6. Medical History (independent of oncological history) including coexisting systemic disease, exercise intolerance, allergies to medications and medication

use, prior illness and surgery, and a thorough review of systems Including the following systems:

a. General (including anorexia, weight loss, cachexia, fatigue, weakness, insomnia)
b. Neurologic (including sedation, confusion, hallucination, headache, motor weakness, altered sensation, incontinence)
c. Respiratory (including dyspnea, cough, pneumonia)
d. Gastrointestinal (including dysphagia, nausea, vomiting, constipation, diarrhea)
e. Psychological (Including irritability, anxiety, depression, dementia)
f. Genitourinary (including urgency, hesitancy, or hematuria)

7. Physical Examination : The physical examination must be thorough although at times it is appropriate to perform a focused examination. In patients with spinal pain, and known or suspected metastatic disease a complete neurologic exam is mandatory. A detailed physical examination can find new evidence of metastatic disease in nearly 64% of patients referred to a Pain Service, resulting in anti-tumor therapy for 18% of patients.

8. Determination of need for further studies.

9. Formulate clinical impression (diagnosis by symptom, ethiology,and mechanism). Multiple diagnosis usually apply and it is optimal to use the most specific known diagnosis. For example: 1) T-11 compression fracture (pathologic versus osteoporotic) with severe pain, 2) Metastatic breast carcinoma (with known bony metastasis), 3) Nausea with inanition, 4) Constipation.

10. Formulate recommendations (Plan) and alternatives for each problem. For example (related to the above problem list): 1) MRI of the T-Spine with consideration of vertebroplasty if appropriate. 2) Oxycodone-slow release 10 mg twice daily, with oral transmucosal fentanyl citrate for breakthrough pain. 3) Management including further chemotherapy, radiotherapy, or bisphosphonates in coordination with the patient's oncologist. 4) Metoclopramide 10 mg po 30 min prior to meals and as needed for nausea. 5) Addition of senekot-S twice daily for constipation.

11. Call oncologist and/or primary care provider if applicable

12. Exit interview

- Explain the probable cause of symptoms in terms the patient can understand.
- Discuss prognosis for symptom relief, management options and specific recommendations. In addition to writing prescriptions, oral and written instructions must be provided. Educational material regarding medications, pain management strategies, procedures, or others should be provided. Potential side effects should be discussed.
- Arrange for follow-up with clinic contact information.
- A dictated summary should be sent to referring and consulting physicians to keep them appraised of the patient's present status and treatment offered.

DIMENSIONAL CLASSIFICATION OF CANCER PAIN

Chronicity

1. Acute Pain: It is frequently associated with sympathetic hyperactivity and heightened distress[33]. It is often temporally associated with the onset or recrudescence of primary or metastatic disease, and its presence should motivate the clinician to seek its cause aggressively and need for more potent analgesics.

2. Subacute Pain: The pain that some patients experience for 4-6 weeks after a major surgical procedure. This type of pain is largely under-treated and deserves special attention as it may affect patient's ability to perform activities of daily living after discharged from the hospital.

3. Chronic Pain: Treating pain of a chronic nature mandates a combination of palliation, adjustment and acceptance. With time, a biological and behavioral

adjustment to symptoms occurs, and hopefully associated symptoms are blunted. Chronic pain with superimposed episodes of acute pain (breakthrough pain) is probably the most common pattern observed in patients with ongoing cancer pain.

Intensity

The consistent use of measurements of pain intensity aids in following a patient's progress and may serve as a basis for inter-patient comparisons. High pain scores may alert the clinician to the need for more aggressive treatment (see figure 1. MDACC treatment algorithm)

Pathophysiology

This approach is useful when formulating the initial approach to treatment.

1. Somatic nociceptive pain is described as a constant, well-localized pain often characterized as aching, throbbing, sharp or gnawing. It tends to be opioid responsive and amenable to relief by interruption of proximal pathways by neural blockade when indicated.

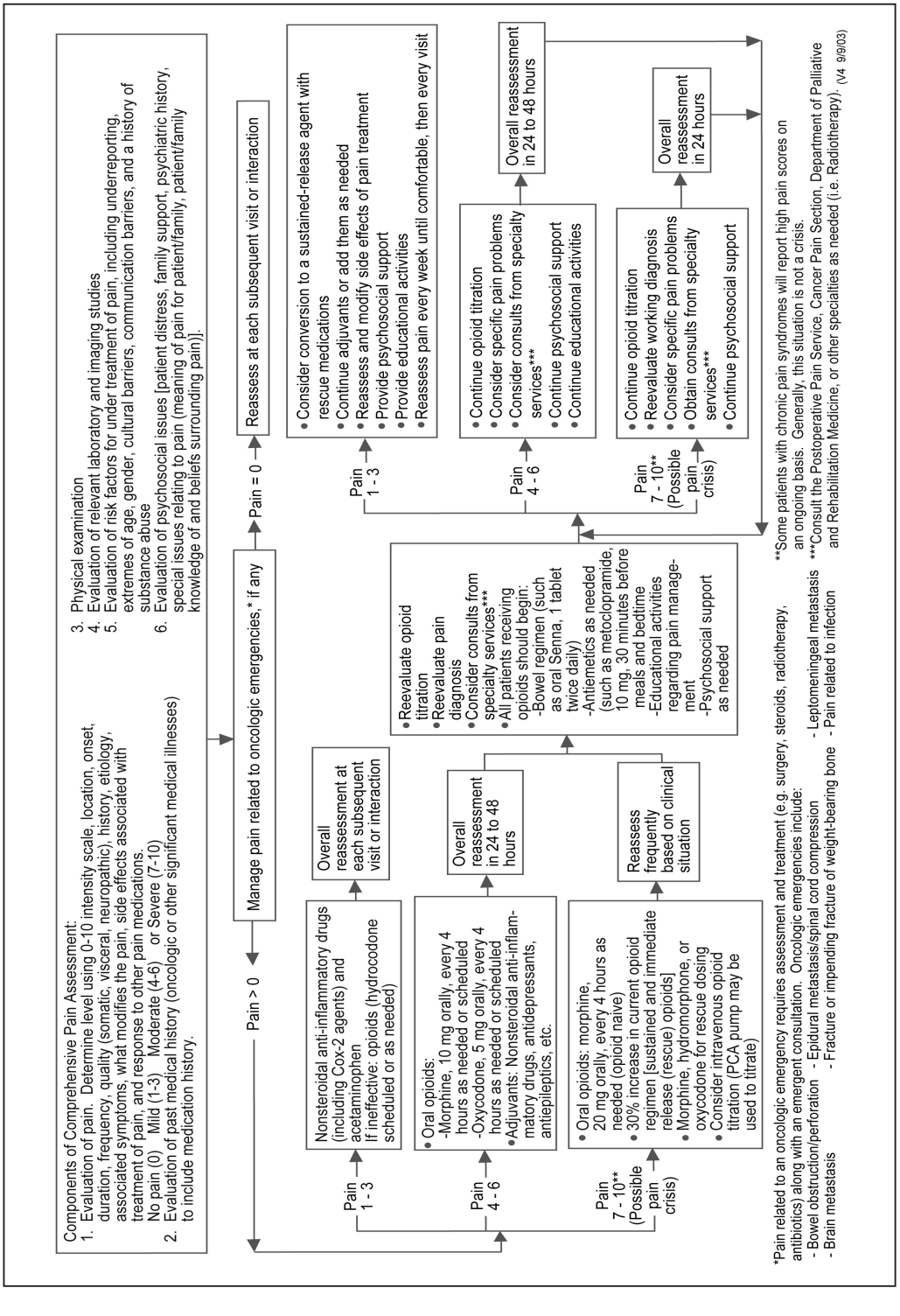
2. Visceral nociceptive pain originates from injury to organs. This pain is transmitted via fibers in the sympathetic nervous system[34]. Visceral pain is characteristically vague in distribution and quality and is often described as deep, dull, aching, dragging, squeezing or pressure like sensation. When acute, it may be paroxysmal and colicky and can be associated with nausea, vomiting, diaphoresis, and alterations in blood pressure and heart rate. Mechanisms of visceral pain include abnormal distension or contraction of the smooth muscle walls (hollow viscera), rapid capsular stretch (solid viscera), ischemia of visceral muscle, serosal or mucosal irritation by algesic substances and other chemical stimuli, distension and traction or torsion on mesenteric attachments and vasculature, and necrosis[35] . The viscera are, however, insensitive to simple manipulation, cutting and burning[34]. Visceral involvement often produces referred pain[36, 37] (e.g. phrenic nerve-mediated shoulder pain of hepatic origin).

3. Neuropathic pain is defined as pain emanating from the nervous system due to injury or irritation to some element of the nervous system. Examples of neuropathic pain syndromes associated with cancer are depicted in Table 1.

Table 1. **Examples of Neuropathic Pain Syndromes**

Example of Neuropathic Cancer Pain Syndromes	
Due to Tumor Growth or Humoral Activity	• Paraneoplastic Polineuropathies • Brachial Plexus Plexopathy • Lumbar Plexus Plexopathy • Skull Base Syndromes • Spinal Cord Compresion
Due to Surgical Nerve Trauma	• Post Thoracotomy Pain • Post Mastectomy Pain • Post Amputation /Phantom Pain
Due to Medical Treatment	• Post Chemotherapy Neuropathies • Post Irradiation Brachial Plexopathy

Figure 1. **MDACC treatment algorithm**



Neuropathic pain is often resistant to standard analgesic therapies and often requires an approach utilizing opioids, anticonvulsants, oral or topical local anesthetics, corticosteroids, NMDA blockers and others.

Temporal aspects of Pain:

1. *Constant Pain*: This pain is most amenable to drug therapy administered around the clock, contingent on time rather then symptoms. It is best managed by long-acting analgesics or in selected cases, infusion of analgesics.

2. *Breakthrough Pain and Incident Pain*: Breakthrough pain that is related to a specific activity, such as eating, defecation, socializing or walking is referred to as incident pain. Breakthrough pain is best managed by supplementing the preventative around-the-clock regimen with analgesics with a rapid onset of action and a short duration. Once a pattern of incident pain is established, escape or rescue, doses of analgesics can be administered in anticipation of the pain provoking activity. Breakthrough pain that occurs consistently prior to the next scheduled dose of around-the clock opioids is called "end of dose failure" and is related to the decrease in plasma concentrations of the analgesics below minimum effective analgesic concentrations (MEAC). "End of dose failure" is ideally managed by increasing the dose of the basal analgesic or reducing the intervals between doses. Refractory incident pain often is responsive to stabilization, such as fixation of a pathologic fracture or vertebroplasty for a vertebral compression fracture.

3. *Intermittent Pain*: This is very unpredictable and can be best managed by administration of immediate release potent analgesics of rapid onset and short duration.

Specific Cancer Pain Syndromes

1. Osseous invasion or tumor infiltration of the bone is cited as the most common cause of cancer pain and is most often seen in metastatic carcinoma of the prostate, breast, thyroid, lung, or kidney[39-41]. The presentation of bone metastatic pain is variable; usually a constant deep dull ache, often greatest at night and with movement or weight bearing, complicated by paroxysms of stabbing pain. Approximately 25% of patients with bone metastasis experience severe pain. Somatic and sympathetic fibers carry pain[42,43]. A bone scan (Isotope Scanning, Scintigraphy) is preferred for detecting most bone metastasis[39].

Prostaglandin E2 (PGE2) and other cytokines are elaborated by osseous metastasis. These cytokines are felt to contribute to pain by sensitization of peripheral periosteal nociceptors in addition to causing central sensitization. NSAIDs and steroids are postulated to reduce pain from bony metastasis via inhibition of the cyclooxygenase pathway of arachidonic acid breakdown, thus decreasing the formation of PGE2. The cox-2 selective anti inflammatories have been shown in a murine sarcoma bone metastasis model to effectively inhibit spontaneous and movement related bone pain, reduce biochemical markers of peripheral and central sensitization, reduce tumor induced osteoclastic proliferation, and finally to reduce overall tumor burden[42-44]. As deposits enlarge, stretching of the periosteum, pathological fracture and perineural invasion contribute to pain and requirements for analgesics increase. Palliative radiation is commonly successfully employed to relieve pain emanating from bony metastasis. Hormonal therapy (chemotherapy such as tamoxifen or leuprolide, orchiectomy, or rarely hypophysectomy) often reduces bony pain in patients with hormonal dependant disease (Breast, Prostate). In general, the hormone refractory breast and prostatic carcinomas are less responsive to treatment [45,46].

2. Vertebral body metastasis is most commonly associated with metastatic carcinoma of the lung, breast and prostate. Localized paraspinal, radicular or referred pain is usually the first sign of metastasis to the bony vertebral column. The pain is often described as severe local, dull, steady, aching, often

exacerbated by recumbence, sitting, movement and local pressure; may be relieved by standing; local midline tenderness may be present; associated nerve compression may produce radiating dermatomal pain and corresponding neurological changes. A special warning must be made here to avoid the most undesirable complication of vertebral body metastasis, that can be avoided in most cases simply by suspiction and a routinely performed neurological examination: an epidural-spinal cord compression[47].

3. Base of skull metastasis: Usually present with headache and a spectrum of neurological findings, especially involving cranial nerves. Symptomatic metastasis to the skull is usually - but not always- a late finding[48]. Plain X-ray, Scintigraphy, and CT scan are helpful for diagnosis of bony disease, while MRI and lumbar puncture are useful to evaluate the soft tissue and to detect leptomeningeal disease, respectively[49].

4. Visceral pain is usually seen in gastrointestinal malignancies due to direct tumor and invasion of visceral structures. This pain is transmitted via fibers in the sympathetic nervous system[34]. Visceral pain is characteristically vague in distribution and quality and is often described as deep, dull, aching, dragging, squeezing or pressure like sensation. When acute, it may be paroxysmal and colicky and can be associated with nausea, vomiting, diaphoresis, and alterations in blood pressure and heart rate. Mechanisms of visceral pain include abnormal distension or contraction of the smooth muscle walls (hollow viscera), rapid capsular stretch (solid viscera), ischemia of visceral muscle, serosal or mucosal irritation by algesic substances and other chemical stimuli, distension and traction or torsion on mesenteric attachments and vasculature, and necrosis[34,35]. Visceral involvement often produces referred pain[36,37] (e.g. phrenic nerve-mediated shoulder pain of hepatic origin). The classic cancer visceral pain syndrome is pancreatic cancer related pain. This pain is described as relentless, mid-epigastric aching, which radiates through to the mid-back, often relieved by the fetal position and worsened by recumbence. These visceral pains can be extraordinarily helped with sympathetic visceral neurolytic blockade[50,51].

5. Musculo-skeletal pain is probably under diagnosed in cancer patients. Underecognition is probably due in part to the inability of standard radiographic technique to document muscle injury, as well as the varied, sometimes vague, and usually non-neurological constellation of characteristic symptoms.

6. Nerve invasion: Typically constant, burning dysesthetic pain, often with an intermittent lancinating, electrical component; may be associated with neurologic deficit or diffuse hyperesthesia or hypesthesia and localized parasthesia; muscle weakness and atrophy may be present in mixed or motor nerve syndromes[52-55].

7. Leptomeningeal metastasis, meningeal carcinomatosis: Most common with primary malignancies of breast and lung; lymphoma and leukemia; it is secondary to diffuse infiltration of meninges; About 40% of patients have headache or back pain, presumably due to traction on the pain-sensitive meninges, cranial, and spinal nerves and/or raised intracranial pressure[56,57]. Headache is most common presenting complaint; characteristically unrelenting; may be associated with nausea, vomiting, nuchial rigidity and mental status changes[57]; associated neurological abnormalities may include seizures, cranial nerve deficits, papilledema, hemiparesis, ataxia and cauda syndrome; diagnosis confirmed with lumbar puncture and CSF analysis, which revealed the presence of malignant cells, and may also be remarkable for an increased opening pressure, raised protein, and decreased glucose[58]. CT or MRI are also recommended and may reveal plaque-like tumor. The natural history of patients with leptomeningeal metastasis is gradual decline and death over 4-6 weeks, although survival is often extended to 6 months or more when treatment with radiation therapy and/or intrathecal chemotherapy is instituted[59]. Steroids may be useful in the management of headache[49].

8. Spinal cord compression is usually heralded by pain in the presence of neurological changes. An urgent radiological work-up in mandatory in the face of neurological deficits, particularly motor weakness, band-like encircling pain or incontinence. Prompt treatment in form of radiotherapy or spinal stabilization may limit neurologic morbidity[47] .

9. Plexopathies are syndromes of tumor invasion into the nerve plexus in the upper of lower extremity. Cervical plexopathy is most commonly caused by local invasion of head and neck cancers or from enlarged lymph nodes. Symptoms are primarily sensory in the distribution of plexus, experiencing as aching pre-auricular, post-auricular, or neck pain. Brachial plexopathy is most commonly due to upper lobe lung cancer (called the Pancoast syndrome or superior sulcus syndrome), breast cancer or lymphoma; pain is an early symptom, usually preceding neurological findings by up to 9 month[52,53], . The lower cord of the plexus (C8-T1) is affected most frequently, and pain is usually diffuse aching in shoulder girdle, radiating down arm, often to the elbow and medial (ulnar) aspect of the hand[54,55]. When the upper trunk is involved (C5-6), pain is usually in the shoulder girdle and upper arm, radiating to the thumb and index finger. Horner's syndrome, dysesthesias, progressive atrophy, and neurological impairment (weakness and numbness) may occur. In some situations the clinical presentation may be difficult to differentiate from radiation fibrosis, which characteristically is less severe, less often associated with motor changes, tends to involve the upper trunks, and may be associated with lymphedema[52,60] without a Horner's sign. Brachial plexus invasion may be associated with contiguous spread to the epidural space[60-62]. Lumbo-sacral plexopathy may be due to local soft tissue invasion or compression occur most commonly with tumors of the rectum, cervix, breast, sarcoma, and lymphoma; pain is usually the presenting symptom in 70% of patients[63]; The pain is usually described as aching or pressure-like and only rarely dysesthetic. Depending on the level involved, pain is referred to the low back, abdomen, buttock, or lower extremity[63, 64]. Reflex asymmetry and mild sensory and motor changes when present, were relatively early findings, whereas impotence and incontinence are relatively rare. This syndrome must be differentiated from spinal cord invasion or cauda equina syndrome in which urgent diagnosis and treatment is mandatory.

10. Chemotherapy Related
    a. Oral mucositis usually occurs in 1-2 weeks of the initiation of chemotherapy. This condition is most common with the use of methotrexate, doxorubicin, daunorubicin, bleomycin, etoposide, 5-fluorouricil, and dactinomycin[65] . Mucositis is often most severe when chemotherapy is combined with radiation treatments to the head and neck region.
    b. Painful polyneuropathy occurs most commonly with vincristine (motor and sensory involvement), vinblastine, taxol taxotere, the platinum derivative (predominantly sensory involvement), and navelbine[66]; Symptoms commonly include burning, dysesthetic pain in the hands and feet.

11. Post-surgical chronic pain syndromes are most common after mastectomy, thoracotomy, radical neck dissection, nephrectomy and amputation[67]. The clinical characteristics usually include aching, shooting, or tingling pain in distribution of peripheral nerves (e.g. intercostals-brachial, intercostals, cervical plexus) with or without skin hypersensitivity. In one of the study[68], the incidence of post-mastectomy pain was higher after conservative surgery than modified radical mastectomy (33% versus 17%). In this same study 25 % of patients experienced post-operative phantom breast pain. The exact incidence of post-surgical pain syndromes is unclear, but appears to be in the 25-50% range by some estimates[67].

12. Headache is present in 60% of patients with a primary or metastatic brain tumor, half of who classified as their primary complaint[69]. It is typically steady, deep, dull,

and aching with moderate intensity and that is rarely rhythmic or throbbing. It is usually intermittent and may be worse in the morning and with coughing-straining. Symptoms often improve with radiation therapy, non steroidal anti-inflammatories, or corticosteroids[70-72].

13. Cervicofacial pain syndromes are most common in patients with head and neck cancers. The head and neck are richly innervated by contributions from cranial nerves V, VII, IX, X and upper cervical nerves, so pain varies in character. When cranial nerves are involved, symptoms represent those of trigeminal, glossopharyngeal, and/or intermittent neuralgia, with sudden, severe lancinating pain radiating to the face, throat or ear respectively.

14. Radiation therapy may be associated with both acute and chronic pain syndromes. Acutely, mucositis, cutaneous burns, may be seen. Chronically, post radiation syndromes include osteoradionecrosis, myelopathy, plexopathy, soft-tissue fibrosis, and the emergence of new secondary neurogenic tumors.

TREATMENT

The goal of treatment of cancer pain is to relieve pain by modifying its source, interrupting its transmission, or modulating its influence at brain or spinal cord sites. This can be achieved with various means and combination of following available modalities (see table 2).

Table 2. **Treatment modalities available for Cancer Pain patients**

(A) Antineoplastic Treatment:

(B) Pharmacological Management

1. NSAID's
2. Opioids
3. Adjuvant analgesics
   - I. Adjuvant drug trials
   - II. Antidepressant
   - III. Anticonvulsants
   - IV. Baclofen
   - V. Oral local anesthetics
   - VI. Amphetamine
   - VII. Corticosteroid
   - VIII. N-Methyl-D-Aspartate (NMDA) Antagonists
   - IX. Alpha-2 Adrenergic antagonists
   - X. Others

(C) Interventional Pain Management

1. Continuous subcutaneous infusion of opioids (CSCI)
2. Continuous intravenous infusion of opioids (CII)
3. Neuraxial analgesia – epidural or intrathecal indusions
4. Neural Blockade Techniques
   - Local anesthetic nerve block
   - Neurolytic nerve block
5. Vertebrosplastia
6. Neuromodulation

(D) Behavioral pain management

(F) Home-based and hospice care

Antineoplastic Treatment

The most effective form of treatment of any cancer related pain is treatment of the cancer itself, which in the majority of cases will reduce or eliminate the pain. Once diagnosed, the pathological process responsible for pain can often be altered with surgical extirpation, external beam radiation therapy (targeted fractioned or single-dosed therapy, hemi body or total body irradiation)[73,74], radionuclides (e.g. Strontium-89, Samarium) intrarterial chemotherapy[75], hormonal treatment[76] and even whole-body hyperthermia[77]. The majority of patients require some form of primary analgesic therapy even when pursuing antitumor therapy.

Pharmacological Management

The control of pain involves three basic principles: modifying the source of the pain, altering the central perception of pain, and blocking the transmission of the pain to the central nervous system. In addition, any new pain in a patient with cancer is assumed disease progression or recurrence until proven otherwise.

Oral analgesics are the mainstay of therapy for patients with cancer pain. An estimated 70-90% of patients can be rendered relatively free of pain when straightforward guidelines-based participles applied in a thorough, careful manner [1,3,4,78].

The World Health Organization (WHO) has developed a three-step ladder approach to cancer pain management that relies exclusively on the administration of oral agents and that is usually effective[19,78]. Care must be taken when use of this ladder, as the evidence was not very strong at the time of publication[79], and its use should always be regarded as the pharmacological systemic approach, usually a part of a more comprehensive pain control strategy . When this conservative therapies produce inadequate results, escalating doses or alternative therapy should be sought in the shortest possible time. The role of more invasive forms of analgesia, ranging from parenteral analgesics to neural blockade or neuraxial analgesia, should be considered judiciously thenafter, but never delayed if the cause of pain is locally restricted[50].

Before initiation of therapy, assessment of problems and setting realistic goals that are acceptable to the patient should be established along with a treatment plan and contingencies.

The non-invasive route should be maintained as long as possible for reasons that include simplicity, maintenance of independence and mobility, convenience, and cost. Treatment should be directed towards relief of pain and suffering, which includes consideration of all aspects of function (e.g. disturbance of sleep, appetite, mood, activity, posture, and sexuality), and attention should be paid not only to physical but also to emotional, psychological, and spiritual aspects of suffering.

The University of Texas MD Anderson cancer Center published a modified and condensed version of the National Cancer Centers Network (NCCN) guidelines, the general strategy is of stronger opioids and adjuvants use with more frequent reassessment for higher pain levels. Some basic principles to manage large population of patients are described here as pearls for cancer pain therapeutics.

1. Nonsteroidal anti-inflammatory drugs (NSAID's)

NSAID's are most effective for pain of inflammatory (eg. bone metastasis) origin by virtue of interference with prostaglandin (PG) Synthesis[80]. Consider the regular (around-the-clock) administration of an NSAID as the sole treatment for mild pain or in combination with opioid analgesic for moderate or severe pain[1]. Potential for benefit should be balanced against potential for toxicity (which includes upper GI irritation, renal insufficiency, platelet dysfunction and masking of fever), which is pertinent in the context of recent antitumor therapy and

advanced age[80]. Consider avoiding NSAID's all together or instituting prophylaxis (e.g. Misoprostol, and proton pump inhibitors as Omeprazol) in patients predisposed to gastropathy.

The nonacetylated salicylate (sodium salicylate, choline magnesium trisalicylate) are associated with a favorable toxicity profile, since they fail to interfere with platelet aggregation, are rarely associated with GI bleeding, and are well tolerated by asthmatic patients[81,82]. A parenteral formulation of ketorolac is equianalgesic to low doses of morphine in some settings but is associated with the same range of side effects as oral NSAID's[83].

NSAID's are associated with s ceiling effects, above which dose escalations produce toxicity but no greater analgesia. However, the ceiling dose for a given drug differs from patient to patient, allowing some potential for dose titration. When efficacy is poor, the clinician may consider rotating to another NSAID, usually from a different biochemical class because it is clear that for a given patient, clinical response differs among various agents (inter-individual variability), and there is evidence that various classes of NSAID's may exert their anti-PG effects on different subtypes of cyclo-oxygenases (COX-1, COX-2)[84], being COX2 the enzyme primarily responsible for peripheral induction of inflammatory sensitization . and partially devoided of the adverse COX1 effects on gastric mucosa, there may be a better safety profile of the newer COX-2 inhibitors in cancer patients versus the traditional NSAIDs, which are non-specific inhibitors of COX-1 and COX-2., with potential advantage in some type of cancers to reeduce tumor burden, but clearly not producing better analgesia than non selective NSAIDs[85] .

2. Opioids

The so-called "Weak Opioids":

When NSAID s are not indicated as per the mechanisms of pain, or if they provide insufficient relief, are contraindicated, are poorly tolerated or when pain is severe at presentation, the addition or substitution of a so-called "weak" opioid (mostly pro-drugs that are metabolized by the patient into small doses of full opioids e.g. codeine, propoxyphene, hydrocodone, or dihydrocodone preparations) is recommended as an analgesic of intermediate potency[1] . These medications are almost exclusively formulated as combination products; these agents are weak only insofar as the inclusion of aspirin, acetaminophen, or ibuprofen results in a ceiling dose above, after which the incidence of toxicity increases.

Also in this category is included Tramadol , a weak agonist that combines its weak opioid effect with potentiating activity by reuptake inhibition of noeadrenaline and serotonin at the presynaptic level. The advantage of this medication may lie in the availability in different presciption presentations as available in Europe (oral solution, capsules and slow release tablets) to better adjust dosage regimen).

While these opioids are appropriate for mild or intermittent pain, physician often rely excessively on these agents, frequently continuing their use after they are no longer effective in an ill-advised attempt to avoid prescribing more potent opioids that are also more highly regulated. The potency of hydrocodone and dihydrocodone preparations is greater than that of codeine and propxyphene[86]. These agents have perceived advantage of not requiring triplicate prescriptions (DEA Class C-III versus C-II in the US), or special duplicated prescribing forms (as a restricted medication in Spain), although the clinician must be cautious not to exceed the usual recommended dose of paracetamol (acetaminophen 4 Gm/day) as opioid requirements increase.

"Potent Opioids":

When combinations of "weak" opioids and adjuvants provide insufficient analgesia or when pain is severe at presentation, more potent opioids should be considered[19]. Morphine, hydromorphone, transdermal fentanyl, and oxycodone are appropriate first-

line opioids for the treatment of moderate to severe pain. Methadone, although inexpensive, and to a lesser extent levorphanol are usually reserved for special circumstances because their half-lives are long and unpredictable, introducing the potential for accumulation, especially in the presence of advanced age and altered renal function[87].

Dosing Guidelines

Pharmacological therapy should be individualized in light of the specific characteristics and needs of each patient[88]. The correct dose of an opioid is the one that effectively relieves pain without inducing unacceptable side effects. Opioids should be initially be introduced in low doses, since the early development of side effects will impair compliance, but they should be rapidly titrated to needed effect. If side effects ensue before adequate pain relief is established, they are treated aggressively in an algorithmic fashion or other strategies should be applied[89, 90] which are described later in this chapter.

a. Calculation of morphine equivalent daily dose (MEDD): If the patient is already on opioid medication, it is recommended to calculate the MEDD in order to administer an equianalgesic dose of an alternate opioid if desired. Opioid dose conversion tables may helpful for calculation, but should be followed cautiously allowing for interpatient variability in opioid side effect sensitivity.
b. Basal and Rescue dosing guidelines: If analgesics are withheld until pain becomes more severe, sympathetic arousal occurs and then even potent analgesics may be ineffective. Thus, a time-contingent schedule for the administration of analgesics is generally preferred to symptom-contingent administration. With prolonged administration on demand, patterns of anticipation and memory of pain become established and may contribute to suffering, even during periods of adequate analgesia. Around-the-clock administration of appropriate analgesics maintains more even therapeutics blood levels and decreases the likelihood of intolerable pain[91]. Compliance and overall quality of analgesia are enhanced by the regular administration of long-acting opioid analgesics for basal pain control, supplemented by a short-acting opioid analgesic administered as needed for breakthrough and incident pain. In practice, controlled-release morphine, controlled-release oxycodone or transdermal fentanyl are available which cannot be broken, crushed or chewed. When these agents are poorly tolerated, methadone or levorphanol may be prescribed, but careful monitoring is required, particularly in elderly patients.
A drug of relatively high potency, short onset, and brief duration, such as immediate-release morphine, hydromorphone, oxycodone, or oral transmucosal fentanyl citrate is selected for as-needed administration to manage exacerbation of pain [92]. These agents should be prescribed every 2-4 hours as needed. When breakthrough medications are used more then 2-3 times over 12 hours consistently, the dose of basal, long-acting analgesic may be increased. If incident pain is a significant problem, the patient should be instructed to take the breakthrough dose in anticipation of pain-provoking activity. A new formulation of oral transmucosal fentanyl citrate has been shown to produce meaningful relief of breakthrough pain within 5 minutes of initiating consumption, an onset that mimics intravenous administration, despite the noninvasive character of this therapy [93] .
c. Agonist-antagonists and Partial Agonists:Agonist-antagonist (Nalbupine, Butorphanol) and partial agonist (buprenorphine) opioid though effec-

tive at the start of strong opioid therapy are generally avoided for a variety of reasons, the most important of which is the presence of a clinical ceiling analgesic effect, or dose above which toxicity but not analgesia increases. However, matrix transdermal presentation of buprenorpine available in Europe may make worthy the utilization buorenorphine in patches to enable gradual titration if intolerance to stronger opioids is severe.

Route of administration

1. Oral: When possible, analgesics should be administered orally or by a similarly noninvasive route (transdermal, rectal, transmucosal) to promote independence and mobility and for ease of titration. In the presence of a functional, intact GI system, once the dose is adjusted to account for the hepatic first-pass effect, oral administration provides analgesia that is as effective as parenteral administration. The sublingual route of adminstration was favored in the hospice setting, but erratic absorption of morphine is problematic. Buccal administration of fentanyl in the form of oral transmucosal fentanyl citrate has become a valuable option for rapid analgesia in patients with severe breakthrough pain[93].

2. Transdermal: When pain control is inadequate with oral analgesics or the oral route is contraindicated, alternative means of drug delivery route should be explored. Transdermal fentanyl provides steady plasma level of analgesic for 72 hours per applied patch. The system's rate-controlling membrane regulates drug release at a slower rate than average skin flux, ensuring that the delivery system rather than the skin is the main determinant of absorption. Temperature is the most important factor in the determinant of absorption, so patients should be cautioned not to place a heating pad directly over the patch. Although low level of fentanyl can be detected in the bloodstream just an hour after administration, a consistent, near-peak level is not obtained for 12-18 hours after treatment is initiated.

3. Rectal: Rectal route is reliable for short-term use except in the presence of diarrhea, fistula, or other anatomical abnormalities. Morphine and hydromorphone are available in rectal preparations in the US, and oxymorphone rectal suppositories provide 4-6 hours of potent analgesia[94]. Rectal methadone is also available in compounded form but should be used judiciously.

4. Other routes of administration: Continuous subcutaneous or intravenous infusions of opioids by means of a pump, IV or subcutaneous PCA, and intrathecal or epidural opioids administered via an externalized catheter or internalized pump can also be used (see interventional pain section below).

Side Effects

Constipation and miosis are the only two opioid-mediated effects to which significant tolerance appears never to develop. Usually a combined mild laxative and softener (Senokot-S) is prescribed when opioid therapy is started. Patients should be instructed about sliding-scale regimen until a regular bowel habit develops. An osmotic agent (e.g. Lactulose) is the usual second-line agent of choice for refractory constipation. Severe constipation may leads to fecal impaction that requires manual disimpaction or the sequential administration glicerine suppositories and lavative enemas to avoid it.

Nausea and vomiting can be so strong that it may require rehydration. Opioid induced nausea and vomiting usually resolves spontaneously with continued opioid use (tolerance to side effects), and thus patients should be reassured and encouraged to adhere to their prescribed regimen of analgesics. The properistaltic agent metoclopramide is our first choice for opioids related emesis, after ensuring constipation is not the cause. Metoclopramide is particularly effective when gastric stasis is suggested by nausea, bloating and early satiety. Haloperidol, prochlorperazine, or chlorpromazine are other reasonable choices, especially when cost is in consideration[89]. Ondansetron, a 5-HT3 anatagonist is com-

monly used as an adjunct to emetic chemotherapies, is sometimes useful, but is very expensive. Dronabinol and corticosteroids are other treatments for refractory nausea.

Opioid induced sedation that fails to improve with time can often be managed effectively with a psychostimulant such as methylphenidate or dextroamphetamine[90].

When side effects are refractory to above mentioned medications trials, opioid rotation should be considered, since side effects are often idiosyncratic and may not be triggered by agents that are in other respects quite similar. If patients have persistent refractory side effects, more invasive modalities should be considered.

Opioid addiction is always a fear in patients receiving opioid medication, which is defined as a psycho-behavioral phenomenon with possible genetic influence characterized by overwhelming drug use, nonmedical drug use, and continued use despite the presence or threat of physiological or psychological harm. Physicians should be able to differentiate addiction from tolerance, which is defined as the need for increasing dosages over time to maintain a desired effect, and physical dependence, a state characterized by the onset of characterized withdrawal symptoms when a drug is precipitously stopped or a specific antagonist is administered. Tolerance and physical dependence are biophysical phenomenon that are inevitable and should be regarded as pharmacological effects. Patient and family education should clarify these issues to aid in patient compliance with the prescribed regimen. This education is an essential element of a successful pain relief program.

Chronic administration of meperidine (also known as petidine) , leads to accumulation of normeperidine, a metabolite that may lead to frank seizure activities, especially when renal function is impaired[95]. Thus, meperidine has fallen from favor as a useful analgesic agent in the treatment of cancer related pain.

3. Adjuvant analgesics

The aim of adjuvant therapy is to elicit an additive or synergistic effect or to diminish the toxicity of the primary therapy. In context of cancer pain, either it enhances opioid-mediated analgesia, diminishes opioid-mediated side effects or improves other symptoms associated with cancer[96]. This analgesics are heterogeneous group of medications originally developed for purposes other then relief of pain that have observed to promote analgesia in specific clinical settings.

It is important fact to remember that (a) Not every agent belonging to each component drug class appears to posses analgesic properties, (b) even agents with confirmed analgesic properties relieve only specific types of pain derived from specific selected conditions and (c) even then, pain relief does not accrue in all affected patients. A brief summary of these drugs is presented here:

I. Sequential drug trials: The recognition that neuropathic pain often fails to respond adequately to the routine administration of opioid and often responds in a binary fashion (no response or partial response) to many adjuvants titrated over time, underlies the contemporary concept of sequential trials. Candidates are best initiated singly in low doses and titrated upward over time (2-4 weeks) until analgesia is achieved, side effects supervene, or the agent under trial can be excluded and a new trial can be commenced[96] .

II. Antidepressants: The efficacy of selected antidepressant as analgesics per se, independent of their effects on mood and nighttime sleep, has been demonstrated mostly in non-cancer models, although utility has been demonstrated for some agents in cancer patients as well[97-104]. The antidepressant characteristically induce analgesia in responders with doses generally considered insufficient to relieve depression argues for a direct, independent underlying mechanism of effect. In addition, although onset is not immediate, analgesia is generally established more rapidly than are antidepressant effects (typically 3-7 days versus

14-21 days). The operant mechanism for antidepressant-mediated analgesia presumably relates to increased circulating pools of norepinephrine and serotonin induced by reductions in the postsynaptic uptake of these neurotransmitters. It is also observed that co-administration of at least Amitriptyline and Clomipramine increases plasma morphine levels[103] .

Tricyclic antidepressants are used for patients with neuropathic pain (e.g. postherpetic neuralgia, central pain, diabetic neuropathy), headache, arthritis, chronic low-back pain, and psychogenic pain[96]. The main indication is neuropathic pain that is relatively constant and unrelenting and that is not predominantly intermittent, lancinating, jabbing, or shocklike. Paroxysmal neuropathic pain may also be treated effectively with tricyclic antidepressants but is often first treated with an anticonvulsant.

Amitriptyline and to a lesser extent imipramine remain the most extensively studied of these agents, and as a result they are the usual first choices. Although relatively innocuous, side effects are especially prominent with these agents. Their metabolites include nortriptyline and desipramine which both have a better side effects profile. Some physician may prefer to start with nortriptyline or desipramine as a first line therapy. Since newer the newer class of antidepressants, the SSRIs (fluoxetine, paroxitine, sertraline, and others) are less effective for treating pain then above-mentioned agents, they may have efficacy in treating depression associated with pain.

Usually amitriptyline, nortriptyline, or desipramine is started at 10-25 mg nightly and gradually titrated upward, usually to a range of 50 to 125 mg and occasionally higher, until toxicity occurs or analgesia is established. Dry mouth, constipation, drowsiness, and dysphoria are the most prominent of a wide range of side effects, which include urinary retention and cardiac dysrhythmia. Unlike the opioids, the development of tolerance is less robust, and side effects are less readily reversible. So if side effects are more prominent then analgesia, the offending agent is usually discontinued and a pharmacological analog or a drug from another class is started. The newer SSRI's may be preferred over the heterocyclic agents for fragile elderly patient, or in patients predisposed to developing anticholinergic side effects, patients whom multiple trials of tricyclics have failed because of side effects, and when depression is a prominent co-morbidity.

III. Anticonvulsants: Carbamazepine, phenytoin, valproate, clonazepam, and most recently gabapentin, alone or in combination with the tricyclic antidepressants, have been shown to successfully treat neuropathic pain[104]. Most authorities consider them as first choice for neuropathic pain and second-line therapy for relatively steady, constant neuropathic pain when tricyclic antidepressants are poorly tolerated, ineffective, or only partially effective[96]. Anticonvulsants dampen ectopic foci of electrical activity and spontaneous discharge from injured nerves, in a manner analogous to their salutary effects in seizure disorders.

Although carbamazepine therapy has been most thoroughly studied anticonvulsant for the treatment of neuropathic pain, it has largely been replaced by the newer and safer anticonvulsants including gabapentin. Gabapentin is a newer anticonvulsant and considered efficacious and well tolerated for neuropathic pain[105] . It should be started by tolerance in doses at 300 to 600 mg per day and subsequently increased up to a maximun of 900 mg three or four times a day until analgesia obtained or side effects developed. Occasionally, patients respond to much higher doses of gabapentin without side effects. Felbamate is also known to interact with NMDA receptors, but its use is limited secondary to aplastic anemia. Other well tolerated newer anticonvulsants include topiramate, levitiracetam, tiagabine, oxcarbazepine, lamotrigine, and zonisamide, but their use on this indication has not been extensively studied.

IV. Baclofen: Baclofen is a g-amino butyric acid (GABA) agonist, which although generally used for spasticity, has

been reported to be effective for lancinating, tic like neuropathic pain. It is usually started at 5 mg twice or three times day or and may be titrated up to 30-90 mg/day, as tolerated. It is also useful for spasticity; especially due to spinal cord injury and multiple sclerosis in the intrathecal route[106].

V. Oral local anesthetics: Oral mexiletine is drug from the class III anthiarrytmics used initially as a disproved diagnostic intervention in neuropathic pain, and later as an adyuvant, usually regarded as a third-line association agent for continuous or intermittent neuropathic pain disorders. Acting as a non-selective Na^+ channel blocker , several studies have shown disappointing efficacy and an important rate of side effects when use in dosis greater than 300 mg a day. No other oral local anesthetic is currently recommended

VI. Amphetamines: The most widely accepted use for amphetamines in the treatment of cancer pain is as a means to reverse opioids induced sedation[107]. Research suggests that dextroamphetamine and methylphenidate possess some analgesic properties and are excellent antidepressants[108]. The amphetamines are well tolerated by cancer patients and instead of inducing anorexia, these agents typically have a paradoxical effect of increasing appetite by enhancing alertness. Nervousness and agitation are the most common side effects.

VII. Corticosteroids: Corticosteroids are known for its efficacy for treatment of acute pain resulting from raised intracranial pressure and spinal cord compression secondary to its effect in reducing peritumoral edema and inflammation with consequent relief of pressure and traction on nerves and other pain-sensitive structures. Improvements in symptoms are often rapid and dramatic but usually depend on continued administration. This effects are short-lived and usually level off in few weeks.

Dexamethasone is the usual drug of choice because it has less potent mineralocorticoid effects. Side effects ranged from dysphoria and diabetes mellitus to florid psychosis. For oncologic emergencies, 100 mg of dexamethasone should be administered as bolus dose, followed by intravenous maintenance dose. The large bolus dose produces severe but transient perineal burning via unknown mechanism. For non-emergencies, dose is 2-6 mg three or four times a day.

VIII. N-Methyl-D-Aspartate Antagonists: The NMDA receptor has been well described and implicated in the transmission of pain. Ketamine and dextromethorphan, partial NMDA antagonists, appear to mediate pain by this mechanism. Subanesthetic doses of ketamine have been administered for prolonged periods with fair success in a small number of patients with refractory neuropathic cancer pain[109,110]. Because of side effects, ketamine infusion should be reserved as a late treatment for highly refractory neuropathic pain.

IX. Alpha-2 Adrenergic antagonists: The centrally acting antihypertensive clonidine has been observed to promote analgesia for neuropathic pain when administered near the neuraxis. Epidural administration has received U.S. Food and Drug Administration (FDA) approval. In a prospective randomized study of 38 patients with severe cancer pain[111] that persisted despite large doses of spinal opioids, the addition of epidural clonidine was associated with significant improvement in 45% of patients overall and 56% of patients with neuropathic pain. Hypotension during the initiation and rebound hypertension during withdrawal are the main potential risk of treatment.

X. Other adyuvants: Strontium is an analogue of calcium and is taken up by the skeleton into active sites of bone remodeling and metastasis. A large clinical trial demonstrated that a 10 micro curie IV dose was an effective adjuvant to local radiotherapy, and that it reduced disease progression, decreased new sites of pain, and decreased systemic analgesics use[112]. It is also a useful adjuvant for diffuse metastatic bone pain. The latency of response can be as long as 2-3 weeks, in which case patients must be instructed to continue analgesic therapy.

The biphosphonate pamidronate disodium, inhibits osteoclastic bone resorption and has been shown to reduce pain and skeletal complications, such as pathological fracture in breast cancer patients and multiple myeloma[113,114]. The drug is administered in a 90 mg intravenous infusion in 2 hr approximately every 4 weeks. Excellent reviews of the literature on this topic are easily available and recommended to read[115].

Interventional Pain Management

When a comprehensive trial of pharmacological therapy fails to provide adequate analgesia or leads to unacceptable side effects, consideration should be given to alternative modalities.

1. Continuous subcutaneous infusion of opioids (CSCI): It is an excellent option for patients whose medical condition precludes the use of the oral route or whose pain is poorly controlled despite large doses of oral opioids[116, 117].

Starting doses are calculated based on the 24-hour dose requirement of intravenous morphine with a conversion table and divide it by 24, which gives the hourly rate. Tissue irritation is minimized when volumes under 1 to 2 ml/hour are prescribed (by concentrating the mixture). A 27-gauge butterfly needle is inserted subcutaneously anywhere with the most preferred sites including the infraclavicular fossa or chest wall for the ease of ambulation.

Absorption of subcutaneously administered opioids is rapid, and steady-state plasma levels are generally approached within an hour[117]. Most parenteral opioids are suitable for CSCI, although morphine and hydromorphone are used most commonly and meperidine, methadone and pentazocine should be avoided because of the potential for tissue irritation. Rescue doses should be given as subcutaneous injection equal to the hourly dose to be administered every 1-2 hour as need.

2. Continuous intravenous infusion of opioids (CII): This modality is indicated in a group of patients include intolerance of the oral route because of GI obstruction, malabsorption, opioid induced vomiting, dysphagia, or the requirement of large number of pills. It is also indicated in a patient getting prominent bolus effect with intermittent injection, the necessity for rapid titration and requirement of bolus injections that exceed nursing capabilities. It is very similar to CSCI, although CSCI is preferred in the home care setting unless a permanent vascular access device is already in place[117] .

Patient controlled analgesia (PCA) is a similar version and excellent option but is reserved for patients with the capacity to understand and use this modification correctly. Dose should be adjusted upward until pain relief is adequate or side effects become intolerable.

3. Intraspinal Analgesia: Neuraxial analgesia is achieved by the epidural or intrathecal administration of an opioids alone or in combination with other agents. With the use of neuraxial analgesia, pain relief is obtained in a highly selective fashion with an absence of motor, sensory, and sympathetic effects, making these modalities highly adaptable to the home care environment[118-122]. The principle of neuraxial opioid therapy is that introducing minute quantities of opioids in close proximity to their receptors (substantia gelatinosa of the spinal cord) achieves high local concentrations[119]. With this therapy, analgesia may be superior to that achieved when opioids are administered by other routes, and since the absolute amount of drug administered is reduced, side effects are minimized.

The neuraxis can be accessed via an intrathecal, epidural, or intraventricular approach, although the intraventricular route is used infrequently, primarily for intractable head and neck pain, and then usually when an access device (Ommaya reservoir) is already in place[123]. The most important aspect of this therapy is its reversibility and the reliability and simplicity of advance screening measures to confirm efficacy. Screening can generally be accomplished on an outpatient basis by

observing the patient's response either to a morphine infusion via a temporary percutaneous epidural catheter or a single-shot intrathecal injection. If improved pain control and reduced side effects are sufficiently profound to warrant more prolonged therapy either with temporary catheter for period of days to weeks or replacement with a permanent implanted catheter along with implanted medication deliverable pump.

Chronic administration of epidural opioids can be accomplished by intermittent bolus administered by the patient, family members, nursing personnel, or more commonly by continuous infusion via a standard PCA portable infusion pump connected to the epidural port. Continuous infusion is a preferred means of administration because intervals of pain between injections are avoided. More commonly a combination of epidural opioids and dilute local anesthetics agents have been determined to be safe and are often beneficial for pain that is refractory to opioids alone[124].

Subarachnoid catheter placement is an alternative to epidural administration. Opioids requirements are less than with epidural administration because of more direct access to the spinal cord. Many factors are considered in the decision for an external pump system versus an implantable pump. These include factors that lead us to an external system: a short life expectancy (< 3 months), the need for frequent patient controlled doses (such as with severe incident pain), the need for an epidural infusion (which generally requires infusion volumes too great for the implanted pump), the lack of reprogramming/refilling capabilities near the patient's home, or payor constraints. We use a variety of catheters for our external systems including a tunneled Arrow FlexTip catheter, the Du Pen's epidural catheter, and the Sims epidural portacath.

Factors that lead us to consider an implantable intrathecal pump include: a longer life expectancy (> 3 months), access to pump refill/reprogramming capabilities, diffuse pain (e.g.- widespread metastasis), and favorable response to an intrathecal trial. We use a programmable (Synchromed, Medtronic, Inc., Minneapolis MN) pump for permanent implantation.

A recently published multicenter prospective randomized clinical trial by Smith, et al., compared intrathecal therapy to continued medical management revealing a slight trend toward better analgesia in the intrathecal group (not statistically significant), but improved side effect profile and increased survival in the intrathecal group[125]. Our group reported a significant improvement in pain scores (NRS 7.9 to 4.1) and decrease from 588 mg/day oral morphine equivalents to 294 mg/day following intrathecal analgesia[126].

Neuraxial medication is expensive, particularly as to whether an implanted pump is a justifiable expense in a patient with a limited life expectancy. Two studies evaluated the external versus internal pump, with the ongoing costs of external pump lease and tubing versus the high initial cost of the implanted pump. These analysis show a "break even" point at approximately 3 months[127, 128].

Recently Hassenbusch and colleagues published current practice data on intrathecal medication management. A survey of 413 physicians managing 13,342 pts was performed. It showed a variety of medications being used in the intrathecal pump including: morphine (48%), morphine/bupivacaine (12%), hydromorphone (8%), morphine/clonidine (8%), hydromorphone/clonidine (8%), morphine/clonidine/bupivacaine (5%), morphine/baclofen (3%), and others (< 3%). Other drugs mentioned included: fentanyl, sufentanil, ziconotide, meperidine, methadone, ropivacaine, tetracaine, ketamine, midazolam, neostigmine, droperidol, and naloxone[129].

Side effects in forms of nausea, respiratory depression, pruritus, urinary retention, dysphoria are common for opioid-naïve patients, but are extremely rare in opioid-tolerant individuals[118].

4. Neural Blockade Techniques:
   a. Local anesthetic nerve blocks: Local anesthetic injections can be broadly

classified as being applicable for diagnostic, and/or therapeutic purposes[130-139].

a1. Diagnostic Blocks: Diagnostic blocks help to characterize the underlying mechanism of pain (nociceptive, neuropathic, sympathetically mediated) and to discern the anatomical pathways involved in pain transmission. Its main indication is as a preliminary intervention conducted prior to a therapeutic nerve block or other definitive therapy. This helps the clinician to determine the potential for subsequent neurolysis if indicated. While results often have good predictive value, they are not entirely reliable.

a2. Therapeutic blocks: The role of this block in cancer patients is limited typically because of transient nature of attendant pain relief. Therapeutic injections of local anesthetics, with or without corticosteroid, into trigger points, subcutaneous foci of localized muscle spasm, may provide lasting relief of myofascial pain[134]. This bedside procedure is particularly useful when muscle spasm arise as a result of prolonged bed rest and for pain that follows thoracotomy, mastectomy, or radical neck dissection. Diffuse subcutaneous injection of coricosteroids and local anesthetics may be useful in acute herpes zoster or post-herpetic neuralgia. Epidural steroid-local anesthetics injection are unlikely to provide lasting relief for back pain due to progressive neoplastic lesions. Local anesthetic injections administered in a series may contribute to lasting pain relief in the setting of post-traumatic sympathetically maintained pain (e.g. reflex sympathetic dystrophy or complex regional pain syndrome)[135-137]. Although infrequent, such symptoms may arise as a result of tumor invasion of nervous system structure (e.g. brachial or lumbosacral plexopathy), in which case either local anesthetic blockade of the stellate ganglion or lumbar sympathetic chain has been used with some success to relieve pain.

b. Neurolytic nerve blocks: Neurolytic blocks have played an important role in the management of intractable cancer pain. This modality should be offered when pain persists despite thorough trials of aggressive pharmacological management or when drug therapy produces unwanted and uncontrollable side effects. Patient selection is important, including: (a) severe pain, (b) pain is expected to persist, (c) pain cannot be modified by less invasive means, (d) pain is well-localized, (e) pain is well-characterized, (f) pain is not multi-focal, (g) Pain is of somatic or visceral origin, (h) patient with limited life expectancy.

Alcohol and Phenol are the only agents commonly used to produce chemical neurolysis. Ethyl alcohol is a pungent, colorless solution that can be readily injected through small-bore needles and that is hypobaric with respect to CSF. For peripheral and subarachnoid blocks, alcohol is generally used undiluted (referred to as 100% alcohol, dehydrated alcohol, or absolute alcohol), while a 50% solution is used for celiac plexus block. It should not be exposed to atmosphere, because absorbed moisture dilutes it. Alcohol injection is typically followed by intense burning pain and occasionally erythema along the targeted nerve distribution. Denervation and pain relief sometimes accrue over a few days following injection.

Phenol is fairly unstable at room temperature. It lasts at least one year when refrigerated and kept away from light. Phenol can be used in 3-15 % concentration and with saline, water, and glycerol or radiological dye. It is relatively insoluble in water, and as a result concentration in excess of 6.7 % cannot be obtained at room temperature without adding glycerine to increase its solubility in water. Phenol with glycerine is hyperbaric (versus alcohol being hypobaric) in CSF, but is so viscid that even when warmed, it is difficult to inject through needles smaller then 20 gauge. Phenol has a biphasic action-its initial local anesthetic action produces subjective warmth and numbness that usually give way to chronic denervation over a day's time. Hypoalgesia after phenol typically is not as dense as after alcohol, and quality and extent of analgesia may fade slightly within the first 24 hours of administration.

Subarachnoid (intrathecal) injections of alcohol or phenol continue to play an important role in the management of intractable cancer pain in carefully selected patients. Neurolytic neuraxial block produces pain relief by chemical rhizotomy. Since alcohol and phenol destroy nervous tissue indiscriminately careful attention to the selection of the injection site, volume and concentration of injectate, and selection and positioning of the patient are essential to avoid neurological complications[139-141]. Most authorities agree that neither alcohol nor phenol offers a clear advantage except insofar as variations in baric properties facilitate positioning of the patient[142,143]. Except for perineal pain, alcohol is usually preferred, since most patients are unable to lie on their painful side, as is required for intrathecal phenol neurolysis. In one of the analysis of 13 published series documenting treatment with intrathecal rhizolysis of more than 2500 patients Swerdlow reported that 58% of patients obtained "good" relief; "fair" relief was observed in an additional 21%, and in 20% of patients "little or no relief" was noted[142]. Average duration of relief is estimated at 3 to 6 months, with a wide range of distribution. Reports of analgesia persisting 1 to 2 years are fairly common[144]. In representative series using alcohol (n= 252) and phenol (n = 151), a total of 407 and 313 blocks were performed respectively [145,146]. In these two series, neither motor weakness nor fecal incontinence occurred, and of 8 patients with transient urinary dysfunction, incontinence persisted in just 1.

Subarachnoid neurolysis can be performed at any level up to the mid-cervical region, above which the risk of drug spread to medullary centers and the potential for cardiorespiratory collapse increases[147]. Blocks in the region of the brachial outflow are best reserved for patients with preexisting compromise of upper limb function. Similarly, lumbar injections are avoided in ambulatory patients, as are sacral injections in patients with normal bowel and bladder function. Hyperbaric phenol saddle block is relatively simple and is particularly suitable for many patients with colostomy and urinary diversion. Until recently, epidural neurolysis was performed infrequently. Results were inferior to those obtained with subarachnoid blockade, presumably because the dura acts as a barrier to diffusion, resulting in limited contact between the drug and targeted nerves[144, 148].

Sympathetic blockade also produces prolonged relief of pain in cases where the pain is sympathetically mediated[135,136] . When local anesthetic sympathetic blocks provide only temporary relief or when clinical findings suggest visceral or sympathetically mediated pain, consideration of chemical sympathectomy is warranted.

Celiac plexus block continues to be one of the most efficacious and common nerve blocks employed in patients with cancer pain[130]. It has great potential for relieving upper abdominal and referred back pain secondary to malignant neoplasm involving structures derived from the foregut (distal esophagus to mid-transverse colon, liver, biliary tree, and adrenal glands). The most common indication for celiac axis block is pancreatic cancer. Celiac axis block is most

commonly performed by positioning needles bilaterally either antero- or retrocrurally via a posterior percutaneous approach

The retrocrural technique is more accurately called a splachnic nerve block. Despite the proximity of major organs (aorta, vena cava, kidneys, pleura) and the requirements for a large volume of neurolytic (30-50 ml of 50% alcohol in the anterocrural technique, much less volume in the retrocrural) complication rates are uniformly low, although some complications are serious[149-151]. In contemporary practice most authorities consider radiological guidance mandatory to verify needle placement[151]. Traditionally fluoroscopy has been used, but CT guidance is increasing in popularity because vascular structures, viscera, and masses can be visualized[152]. Although studies have been criticized for methodological deficiencies, 85 to 94% incidence of good to excellent relief of pain has been obtained in large series of patients undergoing one or more neurolytic celiac plexus blocks for pain from pancreatic cancer, or a variety of intraabdominal neoplasms[153]. In one of the randomized double-blind, placebo-controlled study of intraoperative celiac neurolysis demonstrated that treated patients had not only improved pain control, reduction in opioid use and improved function but also statistically significant improvement in survival[7] . This issue has very recently been submitted again through a well designed methanalysis by the Mayo Clinic group, and has reaffirmed the efficacy in decreasing pain rating within the several weeks after the block, and decreasing the opioid requirements then on . Unfortunately they have not found significant effects in the quality of life indexes when compared to standard pharmachological treatment[50]. Our group at MD Anderson Cancer Center has reported in abstract form a retrospective study revealing an 83% reduction in pain score and 73% reduction in MEDD after splachnic nerve block[154].

Stellate ganglion block, with repeated local anesthetic of the sympathetic outflow to the head, neck, and arm often provide persistent relief of sympathetically maintained pain affecting these regions. Stellate ganglion neurolysis is hazardous because of the close proximity of other important structures (brachial plexus, laryngeal nerves, epidural and subarachnoid space, vertebral artery) and the potential for injury because of inaccurate needle placement. If local anesthetic injections have been documented to provide temporary relief of pain, surgical extirpation of the ganglia may be considered, or neurolysis may be performed cautiously using radiological guidance and small volumes of injectate[155].

Neurolytic lumbar sympathetic block is most applicable for pain in the lower extremities due to lymphedema or reflex sympathetic imbalance, although it has also been applied for rectal and pelvic pain in anecdotal fashion[131].

Superior hypogastric plexus block[156] is generally preferred for intractable chronic pelvic or rectal pain of neoplastic origin. In contrast to subarachnoid injection, risks of bowel, bladder, and motor dysfunction with either lumbar sympathetic or hypogastric block, even when performed bilaterally, are extremely low, particularly with radiological guidance.

In the first published study of superior hypogastric block[156], 28 patients with intrapelvic neoplasms or radiation enteritis were studied, and all had significant or complete relief of pain with no complications. In all but 2 patients with pain due to neoplasm, relief persisted until death (3 to 12 months). In another study of 26 cancer patients with severe (10 out of 10 intensity) intractable pelvic pain: 70% had satisfactory relief (less than 4 out of 10 intensity) and the remaining patients, moderate relief (4 to7 of 10)[157]. Complications were not observed, and no patients with satisfactory relief required repetition out to a 6 month follow up.

The ganglion impar is a solitary retroperitoneal structure at the level of the sacrococcygeal junction that marks the termination of the paired paravertebral sympathetic chains. Although the anatomical interconnections of the ganglion impar are rarely

described in any detail, even in the anatomy literature, the sympathetic component of perineal pain syndromes appears to derive at least in part from this structure. The first report of interruption of the ganglion impar for the relief of anal, genital, or perineal cancer related pain appeared in 1990[158]. Of 16 patients, 8 had complete, durable relief of pain, and the remainder had significant reductions in pain. Blocks were repeated in two patients with further improvement. No complications occurred, and follow-up, which depended on survival, was carried out for 14 to 120 days. The technique entails the use of a 20- or 22-gauge spinal needle that is manually bent near its hub at about 30?. The needle is introduced through the anococcygeal ligament with its concavity oriented toward the concavity of the sacrum and coccyx. Under fluoroscopic guidance the needle is advanced until its tip lies near the anterior surface of the junction of the sacrum and coccyx, posterior to the rectum where injection takes place.

More recently, Radiofrequency-generated thermal lesions are another effective means of inducing therapeutic nerve injury and when directed to the tumor itself, it can have a tumoricidal effect often with salutary effects on symptoms[159] . An optimal result requires the judicious use of fluoroscopy for placement of needle and application of simple but essential adjuncts including the use of a nerve stimulator to avoid the motor root if applicable.

Peripheral/Cranial Nerve Blocks: Peripheral nerve blockade has a limited role in the management of cancer pain[139]. Neoplastic head and neck pain is many times difficult to control because of rich sensory innervations of the structures. In selected patients, blockade of involved cranial and/or upper cervical nerves is very helpful. Blockade of trigeminal nerve within the foramen ovale at the base of skull or its branches may be beneficial for facial pain[160]. If neural blockade is not effective, intraspinal opioid therapy by means of an implanted cervical epidural catheter or intraventricular opioid therapy may be considered[161,162].

5. Vertebroplasty

Many cancer patients with metastatic vertebral or osteoporotic compression fractures(VCFs) present with movement-related back pain. Percutaneous vertebroplasty (PV) is a minimally invasive procedure involving injecting an opacified bone cement (usually polymethymethacrylate or PMMA) into the fractured vertebral body to alleviate the pain and perhaps enhance structural. This procedure is performed by placing needles under fluoroscopic guidance with a uni- or bipedicular approach. PMMA is injected in a carefully controlled manner to avoid unintended cement spread into the spinal canal. Injection is stopped as soon as cement start approaching in posterior on third of vertebral body. PV has been shown efficacious in treating VCF related pain in cancer patients[163].

6. Neuromodulation:

Spinal cord stimulation is widely popularized for refractory neuropathic chronic pain states. It has limited applicability in cancer pain states, except in ongoing chronic neuropathic pain states. Selection of this patient population is very important in cancer group, as MRI is contraindicated after this devise is placed.

Neurosurgical palliative techniques have fallen into less favor as more medications and reversible, titratable, lower risk techniques have largely replaced these procedures. Pituitary ablation entails destruction of the gland by means of the injection of a small quantity of alcohol through a needle positioned transnasally under light general anesthesia. This technique is effective in relieving pain originating from disseminated bony metastases, particularly secondary to hormone-dependent tumors (breast and prostate)[164]. Commissural myelotomy has been reported to be efficacious in cancer pain refractory to more conservative therapy[165]. Percutaneous cordotomy produces a thermal lesion within the substance of the spinal cord and reliably relieves unilateral truncal and lower limb pain [166]. As with pituitary ablation, it necessitates a high degree of skill and expertise, but pain relief

is often profound and the rigors of a major neurosurgical procedure are avoided.

Behavioral Pain Management

Different behavioral pain management techniques have been used in patients with cancer includes hypnosis, relaxation, biofeedback, sensory alteration, guided imagery, and cognitive strategies [167] . Relaxation and imagery training significantly reduce visual analog scale scores in patients who have Mucositis during bone marrow transplant[168]. This training is probably most effective for patients who have no significant psychological or psychiatric problems[169] and in insightful psychology-minded patients.

Home-based and hospice care

For years together, hospice was often incorrectly regarded as a place people go to die, but correctly it is a philosophy of care that is "a blend of clinical pharmacology and applied compassionate psychology"[170,171]. In the United States hospice care has developed primarily as a home based service, with a minority of institutions offering short inpatient stays to stabilize refractory symptoms and to provide respite for overwhelmed families. In Spain, a very well organized Spanish Palliative Care Society (SECPAL) has promoted intensively the creation of palliative care units (hospital, self standing and ambulatory-hospital based units) up to nearly 310 groups distributed across most of the country's geography with great success.

The principles of home-based pain management are in most respects similar to those that apply to ambulatory and inpatient pain management. Differences generally relate to a recognition that further curative therapy is futile rather than that care is being provided at home. No compromise in quality of care based on where it is delivered is justified.

Hospice care is comfort oriented, focusing specifically on alleviating symptoms rather than necessarily treating their underlying cause or causes. Factors that influence the selection of home treatment are advanced, incurable disease, realization and acceptance of the appropriateness of palliative care (care directed at preserving comfort and the quality of life rather than at curing the tumor and extending life), and a desire to die in familiar surroundings. Many difficulties associated with providing intensive palliative care at home can be reconciled by education and orientation of the family and that can be performed with coordination with health care institutions, home care nursing, laboratory, and pharmacy services.

CONCLUSIONS

Palliative Care and Pain management are closely bounded to everyday practice. A basic knowledge update about the current status of concepts and techniques for Cancer pain management is of prime importance for every pactioner caring for Cancer patients as a resource for appropiate information and solution to pain problems of his patients. As presented, Acute and chronic pain occurs in a high frequency of cancer patients. Inadequate assessment and treatment of pain and other distressing symptoms may interfere with primary antitumor therapy and markedly detract from their quality of life . While a strong focus on pain control is important independent of disease stage, it is a special priority in patients with advanced disease who are no longer candidates for potentially curative therapy.

While rarely eliminated altogether, pain can be controlled in the vast majority of patients, usually with the careful application of straightforward pharmacological measures combined with diagnostic acumen and conscientious follow up. In the small but significant proportion of patients whose pain is not readily controlled with noninvasive analgesics, a variety of alternative measures, when selected carefully, are also associated with a high degree of success provided by specialized in pain clinics. An increasingly large number of anesthesiologists, oncologists, and psychologists and

other medical and non-medical professions have come to recognize that far from an exercise in futility, caring for patients with advanced irreversible illness can be a highly satisfying endeavor that is usually met with considerable success. Thus, no patient should ever wish for death or think in euthanasia as a result of inadequate control of pain or other symptoms, and clinicians must never communicate overtly or indirectly that nothing more can be done. Comprehensive cancer care is best regarded as a continuum that commences with prevention and early detection, focuses intensely on curative therapy, and ideally is rendered complete by a seamless transition to palliation and attention of quality of life.

The future of cancer pain relief is bright, as much mechanistic research is looking into different groups of specifically targeted medications including tumor necrosis alpha receptor antagonists, inhibitors of glutamate release, substance P inhibitors, nitric oxide synthetase inhibitors, and other novel compounds.

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