CLINICAL PRACTICE GUIDELINES

Cancer Pain

Ministry
of Health

NMRC
National Medical
Research Council

Mar 2003

MOH Clinical Practice Guidelines 5/2003

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial, as part of the body of literature of overall good quality and consistency, addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies, but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Cancer Pain

MOH Clinical Practice Guidelines 5/2003

Available on the MOH website: http://www.gov.sg/moh/pub/cpg/cpg.htm

Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Cancer is a major source of morbidity and mortality. Besides being the leading cause of death in Singapore, the effects of being struck by cancer are often devastating to the individual and his or her family. One important aspect of cancer morbidity is the associated pain. It is estimated that 60 to 90 percent of patients with advanced cancer have pain. As chronic or severe pain has a profound effect on the patient physically, psychologically and socially, effective management of cancer pain is essential to the patient's wellbeing and quality of life.

These guidelines should provide a welcome aid to doctors who manage patients with cancer. The key messages that are made in these guidelines are that cancer pain represents unnecessary suffering and cancer pain can be controlled in the majority of patients through relatively simple means. Guidance is provided on evaluating cancer pain and the various options for treating it.

I would like to acknowledge the enthusiasm and hard work put in by the workgroup in developing these comprehensive and useful guidelines.

PROFESSOR TAN CHORH CHUAN
DIRECTOR OF MEDICAL SERVICES

Contents

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

General

A Patients and their families should be reassured that most cancer pain can be relieved safely and effectively. (pg 12)

Grade A, Level Ib

A Involvement of a multidisciplinary team of specialists is associated with effective analgesia and better health outcomes. (pg 12)

Grade A, Level Ib

GPP Clinicians should assess patients for pain and provide optimal relief throughout the course of illness. (pg 12)

GPP

Evaluation of cancer pain

A Cancer pain should be comprehensively evaluated because this results in improved analgesia. (pg 14)

Grade A, Level Ib

B Health professionals should routinely ask about pain in cancer patients, and the patient's self-report should be the primary source of assessment. (pg 14)

Grade B, Level III

B An accurate assessment should be performed to determine the type and severity of pain and its effect on the patient prior to treatment. (pg 14)

Grade B, Level III

B A simple formal assessment tool should be used in the ongoing assessment of pain. (pg 15)

Grade B, Level III

B Clinicians should be aware of common pain syndromes, because prompt recognition allows early therapy and minimizes the morbidity of unrelieved pain. (pg 15)

Grade B, Level III

B A thorough assessment of the patient's psychosocial state should be carried out. The clinician should look for anxiety and depression and ascertain the patient's beliefs about his or her pain. (pg 15)

Grade B, Level III

B Attention should be given to cultural and ethnic factors which may have a bearing on the patient's response to pain and pain control. (pg 15)

Grade B, Level III

C Sudden severe pain in patients with cancer should be recognized as a medical emergency and patients should be promptly assessed and treated. (pg 13)

Grade C, Level IV

GPP Clinicians should document the efficacy of pain relief at regular intervals after starting or changing treatment. Documentation forms should be readily accessible to all clinicians involved in the patient's care. (pg 14)

GPP

Principles of cancer pain management

B The principles of treatment outlined in the WHO Cancer Pain Relief Programme should be followed when treating pain in patients with cancer. (pg 20)

Grade B, Level III

B Medications for persistent cancer-related pain should be administered on a round-the-clock basis with additional "as needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain. (pg 21)

Grade B, Level III

GPP The simplest dosage schedules and least invasive pain management modalities should be used first. (pg 20)

GPP

GPP Placebos should not be used in the management of cancer pain. (pg 20)

GPP

Choice of analgesic therapy

B A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain. (pg 22)

Grade B, Level III

B If pain severity increases, the next step of the analgesic ladder should be taken. Another analgesic of the same potency should not be used. (pg 23)

Grade B, Level III

A Pharmacologic management of mild pain should include an NSAID or paracetamol at recommended doses, unless there is a contraindication. (pg 22)

Grade A, Level Ia

A Patients receiving an NSAID who are at risk of gastrointestinal side effects should be prescribed famotidine 40 mg twice a day, misoprostol 200µg four times a day, or omeprazole 20 mg once a day. (pg 22)

Grade A, Level Ib

A When pain persists or increases, an opioid should be added to the analgesic regimen. (pg 23)

Grade A, Level Ia

B All patients with moderate to severe pain should receive a trial of an opioid analgesic, regardless of the aetiology of the pain. (pg 23)

Grade B, Level IIa and IIb

B If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, move to step 3 of the analgesic ladder. (pg 23)

Grade B, Level III

Use of Opioids in the treatment of moderate to severe pain

B The opioid of first choice for moderate to severe pain is morphine. (pg 26)

Grade B, Level III

B The optimal route of administration is by mouth. There should ideally be two types of oral formulations: immediate-release for dose titration and controlled-release for maintenance treatment. (pg 26)

Grade B, Level III

B The opioid dose for each patient should be individually titrated to achieve maximum analgesia and minimum side effects. (pg 26)

Grade B, Level III

C Where possible, opioid dose titration should be carried out with an immediate-release morphine preparation given every four hours to maintain constant levels of analgesia (pg 26)

Grade C, Level IV

A Once suitable pain control is achieved by use of immediate-release morphine, conversion to the same total daily dose of controlled-release morphine should be considered. (pg 26)

Grade A, Level Ib

C Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of immediate-release morphine. The breakthrough dose should approximate one-sixth of the total daily dose of oral morphine. (pg 27)

Grade C, Level IV

C If patients are unable to take opioids orally, the rectal, transdermal or subcutaneous route may be used. There is no indication for use of the intramuscular route for chronic cancer pain because the subcutaneous route is associated with less risk and less pain. (pg 27)

Grade C, Level IV

C The average relative potency ratio of oral to parenteral morphine is 1:3. (pg 27)

Grade C, Level IV

B A small proportion of patients develop intolerable side effects with oral morphine. In such patients a change to an alternative opioid or a change in the route of administration should be considered. (pg 27)

Grade B, Level III

A Transdermal fentanyl is an effective alternative to oral morphine, but is best reserved for patients with stable opioid requirements. (pg 28)

Grade A, Level Ib

C Methadone is an effective alternative drug, but is more difficult to use than other opioids because of pronounced inter- and intra-individual differences in its duration of action and relative analgesic potency. Its use by non-specialist practitioners is not recommended. (pg 28)

Grade C, Level IV

B Patients receiving opioid agonists should not be given a mixed agonist-antagonist because of the risk of precipitating a withdrawal syndrome and exacerbation of pain. (pg 28)

Grade B, Level IIb

B Pethidine should not be used if continued opioid use is anticipated. (pg 29)

Grade B, Level IIa

B Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia, or suffer intolerable side-effects, despite the optimal use of systemic opioids and non-opioids. (pg 26)

Grade B, Level III

Specific issues regarding opioid use

A Specific interventions to treat the adverse effects of opioid therapy are efficacious. (pg 30)

Grade A, Level Ib

B Constipation is a common problem associated with long-term opioid administration and should be treated prophylactically. (pg 30)

Grade B, Level III

B When naloxone is given to reverse opioid-induced respiratory depression, it should be titrated to improve respiratory function, but with preservation of analgesia. (pg 31)

Grade B, Level IIb

C Mental clouding or confusion due to opioid toxicity should be managed by reducing the dose of opioid, ensuring adequate hydration and treating the agitation/confusion with a neuroleptic, such as haloperidol. (pg 31)

Grade C, Level IV

B Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence or addiction. (pg 32)

Grade B, Level III

B Patients prescribed opioids for pain should be reassured that they will not become psychologically dependent on or addicted to their opioid analgesia. (pg 32)

Grade B, Level III

Adjuvant drugs

A Patients with neuropathic pain should have a trial of a tricyclic antidepressant and/or an anticonvulsant. (pg 33)

Grade A, Level Ia and Ib

C A trial of steroids should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, and spinal cord compression. (pg 33)

Grade C, Level IV

Bisphosphonates

A Bisphosphonate treatment should be considered in addition to conventional analgesic techniques for all patients with multiple myeloma, and breast cancer patients who have pain due to metastatic bone disease. (pg 34)

Grade A, Level Ia and Ib

Anti-tumour Therapy

C Systemic chemotherapy should be considered for cancers which are highly chemosensitive. (pg 36)

Grade C, Level IV

C Hormonal manipulation may contribute to pain relief in hormone sensitive cancers. (pg 37)

Grade C, Level IV

C Radiotherapy is effective in relieving pain due to tumour infiltration. (pg 37)

Grade C, Level IV

C When using anti-tumour therapy, concomitant use of effective analgesics must not be neglected. (pg 37)

Grade C, Level IV

Interventional Techniques

C Professionals who manage patients with cancer pain should be aware of the range of interventional techniques available for the relief of pain and have access to a specialist pain clinic providing a range of interventional techniques. (pg 39)

Grade C, Level IV

GPP Non-invasive therapies should precede invasive treatments, except in rare instances. (pg 39)

GPP

A Coeliac plexus block should be considered in patients with upper abdominal pain, especially when secondary to pancreatic cancer. (pg 41)

Grade A, Level Ia and Ib

A Epidural, intrathecal and intraventricular opioids should be considered in treatment of cancer pain not controlled with opioids by other routes. (pg 43)

Grade A, Level Ia and Ib

Non-pharmacologic Management: Physical and Psychosocial Modalities

C Cutaneous stimulation techniques, such as application of superficial heat and cold, massage, pressure and vibration, may provide pain relief when the source of pain is associated with muscle tension or spasm. (pg 45)

Grade C, Level IV

A Patients should be remain active and participate in self-care when possible. (pg 45)

Grade A, Level Ib

B Prolonged bed-rest for cancer patients should be avoided because prolonged immobilization may lead to joint contractures, muscle atrophy, cardiovascular deconditioning, and other undesirable effects. (pg 45)

Grade B, Level III

A Psychosocial interventions should be used concurrently with pharmacological treatment for pain as part of a multidisciplinary approach to pain management and not as substitutes for analgesics. (pg 46)

Grade A, Level Ib

B Education on effective pain control modalities and correction of misconceptions relating to the use of opioids should be a routine part of patient management. (pg 46)

Grade B, Level III

GPP Pastoral care team members should participate in health care team meetings that discuss the needs and treatment of patients. They should be conversant with community resources that provide spiritual care and support for patients and their families. (pg 44)

GPP

Pain in special populations

B Clinicians should give special attention to the assessment and treatment of pain in special populations, including the very young, the very old, the cognitively impaired, and known or suspected substance abusers. Aggressive pain assessment and management are as necessary for them as for the general population. (pg 47)

Grade B, Level III

B Behavioural observation should be the primary assessment method for preverbal and nonverbal children, and used as an adjunct for assessment of verbal children. (pg 48)

Grade B, Level III

B In older children, assessment includes self-report using age-appropriate scales, such as the faces pain scale, and the numeric rating scale. Observation should be used as an adjunct to self-report. (pg 48)

Grade B, Level IIb

C Oral medication in children with cancer pain should follow the WHO analgesic ladder, with dosage adjustments. The basic principles of opioid use are similar to those in adults. (pg 48)

Grade C, Level IV

GPP Assessment in the cognitively intact elderly patient with cancer pain should be done in ways similar to that of the general adult population. (pg 47)

GPP

B Behavioural observation should be an adjunct to cancer pain assessment in cognitively impaired adults. (pg 50)

Grade B, Level III

C Non-opioid analgesic modalities should not be substituted for opioid analgesics to treat severe pain in the suspected or known substance abuser. (pg 50)

Grade C, Level IV

1 Introduction

A Patients and their families should be reassured that most cancer pain can be relieved safely and effectively.

Grade A, Level Ib

A Involvement of a multidisciplinary team of specialists is associated with effective analgesia and better health outcomes.

Grade A, Level Ib

GPP Clinicians should assess patients for pain and provide optimal relief throughout the course of illness.

GPP

1.1 Objectives

The purpose of these guidelines is to:

- optimize pain control in cancer patients
- minimize side-effects, adverse outcomes and costs of pain therapy
- enhance the physical, psychological and spiritual well-being of cancer patients and improve the quality of life of patients and their families.

1.2 Target Group

The guidelines emphasize the need for (1) routine pain assessment, (2) proficiency in prescribing opioids, non-opioid analgesics, and adjuvant medications, and (3) an understanding of the potential benefits of antineoplastic, anaesthetic, neurosurgical, and behavioural modalities, which often require a coordinated multidisciplinary approach.

These guidelines are intended for use by medical practitioners and health care professionals in the multidisciplinary team providing care for patients with cancer. They are applicable to patients of all ages and with all types of cancer.

1.3 Guidelines development

These guidelines were developed by a multidisciplinary workgroup comprising the members of and experts appointed by the Executive Committee of the Pain Association of Singapore, which is also the Singapore chapter of the International Association for the Study of Pain. Because the available data on management of cancer pain in the Singapore context is limited, the workgroup has taken into consideration guidelines and studies from other countries.

1.4 Background

The incidence of pain in patients with cancer depends on the type and stage of disease, although significant and prolonged pain can occur at any stage of the disease. At the time of diagnosis and at intermediate stages, 30% to 45% of patients experience moderate to severe pain[1]. On average, 60% to 90% of patients with advanced cancer have pain[2]. Of cancer patients with pain, 40% to 50% report it as being moderate to severe, and another 25% to 30% describe it as very severe[3]. Multiple sites and causes of pain in individual patients are common, with up to 81% of patients reporting pain in 2 or more sites[4]. In addition, pain associated with cancer therapy occurs in 15% to 25% of patients undergoing chemotherapy, radiotherapy or surgery, a figure that rises to 60% in children undergoing treatment. These figures are paralleled in the Singapore experience[5,6,7,8].

Pain associated with cancer is frequently undertreated in both adults[3,9,10] and children[11], with up to 42% of treated patients complaining of inadequate analgesia. In the series of Jayaratnam et al[8], pain control was achieved in 25%, not attained in 45% and not recorded in the remainder. In another local study[12] pain was present in 82% of cancer patients at the point of referral to a hospice home care service. Pain control was adequate in only 22% of these, and oral morphine mixture was incorrectly prescribed in half of the treated patients.

The World Health Organization (WHO) has emphasized that "nothing would have a greater impact on improving cancer pain treatment than implementing existing knowledge"[13]. These guidelines represent an effort to disseminate knowledge on the assessment and treatment of cancer pain. The individual practitioner involved in the care of these patients must ensure that his or her medical information is current and that patients receive appropriate education.

1.5 The consequences of pain

Cancer pain represents unnecessary suffering. Unrelieved pain destroys the quality of life of patients and may lead to suicide[14]. It interferes with function, movement, endurance, appetite and sleep. This in turn can weaken already debilitated patients. Pain can lead to depression with loss of hope and rejection of active treatment programs. It causes anxiety, fear, loss of concentration, somatic preoccupation and loss of control. Emotional well-being, sexual function, appearance, caregiver requirements and social relationships are adversely affected. Even when the underlying disease is stable, pain prevents productive employment, enjoyment of recreation and pleasure in one's usual role in family and society[15]. Pain is usually considered an ominous symptom by cancer patients; it may or may not signify recurrent or progressive disease, and its significance should be discussed with the patient once accurate diagnosis of its cause is made.

1.6 Effectiveness of available treatment

Cancer pain can be controlled in the vast majority of patients through relatively simple means[16-18]. The WHO has urged that every nation give high priority to establishing a cancer pain relief policy[18]. To this end, it has devised a simple, well-validated, and effective method[19] for assuring the rational titration of therapy for cancer pain. The WHO analgesic ladder (see below) is effective in relieving pain for approximately 90% of patients with cancer[20,21]. This has been validated in many countries and different settings of care. This success rate is, however, not usually achieved in routine clinical practice because of various patient, physician and systemic factors. A multidisciplinary approach to cancer pain improves analgesia as well as other clinical outcomes[22,23].

2 Evaluation of Cancer Pain

A Cancer pain should be comprehensive evaluated because this results in improved analgesia.

Grade A, Level Ib

B Health professionals should routinely ask about pain in cancer patients, and the patient's self-report should be the primary source of assessment.

Grade B, Level III

B An accurate assessment should be performed to determine the type and severity of pain and its effect on the patient prior to treatment.

Grade B, Level III

B A simple formal assessment tool should be used in the ongoing assessment of pain.

Grade B, Level III

B Clinicians should be aware of common pain syndromes, because prompt recognition allows early therapy and minimizes the morbidity of unrelieved pain.

Grade B, Level III

B A thorough assessment of the patient's psychosocial state should be carried out. The clinician should look for anxiety and depression and ascertain the patient's beliefs about his or her pain.

Grade B, Level III

B Attention should be given to cultural and ethnic factors, which may have a bearing on the patient's response to pain and pain control.

Grade B, Level III

C Sudden severe pain in patients with cancer should be recognized as a medical emergency and patients should be promptly seen and assessed.

Grade C, Level IV

GPP Clinicians should document the efficacy of pain relief at regular intervals after starting or changing treatment. Documentation forms should be readily accessible to all clinicians involved in the patient's care.

GPP

The accurate assessment of pain is of paramount importance in the effective control of pain. It is an integral part of overall clinical assessment and is necessary in order to plan appropriate interventions or treatments.

2.1 Pain Assessment

This should be carried out with each new report of pain. The patient's self-report should be the primary source of assessment. The goals of assessment are to:

1. Characterize the pathophysiology of pain
2. Determine its intensity
3. Determine its impact on functional ability
4. Identify factors that may influence the response to analgesia

2.1.1 Initial evaluation

The initial evaluation should include:

1. A detailed history, including a detailed description of the pain (its onset, temporal pattern, location, intensity, aggravating and relieving factors) and the patient's cognitive/emotional response (Table 1).
2. Previous treatment and response.
3. Physical examination with an emphasis on neurological examination, especially when there is suspicion of neuropathic pain or spinal cord lesions
4. Psychosocial assessment (Table 2).
5. An appropriate diagnostic work-up to determine the cause of pain e.g. bone scans, CT scans, MRI.

2.1.2 Subsequent evaluation

There should be ongoing assessment of the patient's pain, and the efficacy of the treatment plan. Pain should be assessed and documented

1. at regular intervals

2. with each new report of pain
3. at suitable intervals after each intervention, e.g. 15 to 30 minutes after parenteral therapy, or one hour after oral therapy.

2.1.3 Causes of pain

There are multiple causes of pain in patients with cancer (Table 3). The type of pain determines therapeutic response to opioids and hence the choice of analgesics. It is important to distinguish between pain caused by stimulation of normal nerve endings by noxious substances **(nociceptive pain)** and pain caused by nerve dysfunction **(neuropathic pain)**. The latter is often associated with altered sensory perception, such as numbness or hypoaesthesia, tingling or parasthesiae, or allodynia (pain sensation caused by a normally non-painful stimulus).

2.2 Standard assessment tools

A logical approach and the use of validated tools help to clarify the different aspects of a patient's pain. Pain assessment tools must measure intensity of pain, relief of pain, psychological distress and functional impairment. Table 4 and Figure 1 shows some of the assessment tools available and their use. Unidimensional measures of pain intensity are commonly used in day-to-day practice.

2.3 Barriers to pain assessment

For effective management of pain, health professionals must be aware of the barriers to and the complexities of pain assessment. These include[24-28]:

- The multidimensional and subjective nature of pain
- The lack of a clearly defined or standardized language to describe pain
- Concurrent anxiety or depression
- Language, ethnic and cultural factors
- Cognitive impairment or reduced conscious level on the part of the individual assessed
- Incorrect attitude and ignorance in health professionals regarding adequate pain control

Table 1 Taking a pain history

1.	**Onset and temporal pattern** When did your pain start? How often does it occur? Is it there all the time or is it episodic? Has its intensity changed over a period of time?
2.	**Location** Where is your pain? Does it run from one place to another? Is there more than one site?
3.	**Description** What does your pain feel like? What words would you use to describe your pain?
4.	**Intensity** On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, how much does it hurt right now? How much does it hurt at its worst? How much does it hurt at its best? Does the intensity fluctuate during the course of the day?
5.	**Aggravating and relieving factors** What makes your pain better? What makes your pain worse? Does it ever come spontaneously?
6.	**Associated symptom** Is the pain associated with any sensory change, such as numbness or hypersensitivity?
7.	**Previous treatment** What types of treatments have you tried to relieve your pain? Were they and are they still fully or partially effective?
8.	**Effect** How does the pain affect physical and social function?

Table 2 Psychosocial factors affecting pain tolerance[29]

Factors that lower pain tolerance	Factors that raise pain tolerance
• Discomfort • Insomnia • Fatigue • Anxiety • Fear • Anger • Boredom • Sadness • Depression • Introversion • Social abandonment • Mental isolation	• Relief of symptoms • Sleep • Rest or (paradoxically) physiotherapy • Relaxation therapy • Explanation/support • Understanding/empathy • Diversional therapy • Companionship/listening • Elevation of mood • Understanding of the meaning and significance of the pain

Table 3 Causes of pain in patients with cancer

Related to tumour

a) Direct infiltration
b) Distant metastases (e.g. bone and brain metastases)
c) Obstruction of hollow organ (e.g. stomach, bladder)
d) Distension of capsule of solid organ (e.g. liver, kidney)
e) Compression (e.g. of the spinal cord)
f) Paraneoplastic pain syndromes (e.g. hypertrophic osteoarthropathy)

Related to treatment of cancer

a) Post-surgery (e.g. post-thoracotomy syndrome)
b) Post-chemotherapy (e.g. mucositis)
c) Post-irradiation (e.g. fibrosis after head and neck irradiation)

Unrelated to cancer or its treatment

e.g. osteoarthritis, degenerative spinal disease, peptic ulcer disease

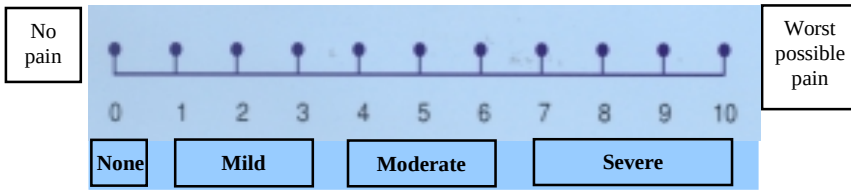
Related to chronic debility

e.g. chronic constipation, deep vein thrombosis, cheilitis, decubitus ulcers

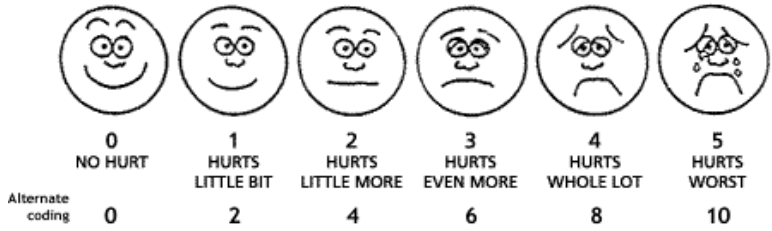
Table 4 Pain assessment tools and their application

Tool	Description/setting
MULTIDIMENSIONAL	
Memorial Pain Assessment Card[30]	A short and simple questionnaire which measures intensity, relief of pain, and psychological distress, developed for use in a hospital setting.
Wisconsin Brief Pain Inventory[31,32]	Measures intensity and relief of pain, psychological distress, and functional impairment. A valid and reliably tested tool translated and validated in many languages. A shortened version has been recommended for use in research.
McGill Pain Questionnaire[32,33]	One of the first assessment tools whose introduction revolutionized pain assessment. The full chart is very detailed and time-consuming to complete. The short-form is recommended for use in research, but it is not available in many languages.
UNIDIMENSIONAL	
Numeric Rating Scale (NRS)	The patient rates pain on a scale from 0 to 10.
Visual Analogue Scale (VAS)[34]	The patient indicates intensity of pain on a 10 cm line marked “no pain” at one end and “severe pain” at the other end.
Verbal Rating Scale (VRS)[34]	The patient rates the pain verbally, as “none”, “mild”, “moderate” or “severe”.
Faces Pain Scale[35,36]	The patient rates pain by pointing to a picture of a face as an indication of pain severity.

Figure 1 Example of a Pain Ruler with the Numeric Rating Scale and Verbal Rating Scale, and the Wong-Baker faces for non-verbal adults and children.



Pain Ruler



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: Wong's Essentials of Pediatric Nursing, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

3 Cancer Pain Therapy

3.1 Principles of cancer pain management

B The principles of treatment outlined in the WHO Cancer Pain Relief Programme should be followed when treating pain in patients with cancer.

Grade B, Level III

B Medications for persistent cancer-related pain should be administered on a round-the-clock basis with additional "as needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain.

Grade B, Level III

GPP The simplest dosage schedules and least invasive pain management modalities should be used first.

GPP

GPP Placebos should not be used in the management of cancer pain.

GPP

Although analgesics are the mainstay of cancer pain management, a multimodal approach to treatment is often necessary.

This multimodal approach involves:

1. Treatment of the neoplastic process by radiotherapy, surgery, and pharmacological therapy, such as antineoplastic chemotherapy, hormonal agents and antibiotics.
2. Optimization of analgesic treatment.
3. Consideration of other treatment approaches with knowledge of the indications and possible complications of specific procedures:
    a. Anaesthetic approaches (e.g. temporary and permanent nerve blocks, intraspinal opioids with or without local anaesthetics)
    b. Neurostimulatory approaches (e.g. transcutaneous electrical nerve stimulation, spinal cord stimulation)
    c. Neurosurgical approaches (e.g. cordotomy)
    d. Physical approaches (e.g. use of orthotics, physical therapy)
    e. Psychological approaches (e.g. training in cognitive approaches, such as relaxation)

4. Awareness of the costs associated with pain treatment and critical evaluation of the utility of drugs, routes of administration and interventional procedures.

Medications for persistent cancer-related pain should be administered on a round-the-clock basis, with additional "as needed or rescue" doses. The aim is to maintain a constant level of drug in the body and prevent recurrence of pain. Rescue doses are given for breakthrough pain[37, 38].

3.2 Choice of analgesic therapy

B A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain.

Grade B, Level III

B If pain severity increases, the next step of the analgesic ladder should be taken. Another analgesic of the same potency should not be used.

Grade B, Level III

A Pharmacologic management of mild pain should include an NSAID or paracetamol at recommended doses, unless there is a contraindication.

Grade A, Level Ia

A Patients receiving an NSAID who are at risk of gastrointestinal side effects should be prescribed famotidine 40 mg twice a day, misoprostol 200 µg four times a day, or omeprazole 20 mg once a day.

Grade A, Level Ib

A When pain persists or increases, an opioid should be added to the analgesic regimen.

Grade A, Level Ia

B All patients with moderate to severe pain should receive a trial of an opioid analgesic, regardless of the aetiology of the pain.

Grade B, Level IIa and IIb

B If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, move to step 3 of the analgesic ladder.

Grade B, Level III

The World Health Organization (WHO) analgesic ladder (Figure 2) consists of a hierarchy of oral medications designed to treat effectively pain of increasing magnitude[39]. It is not meant to be a rigid framework, but may be varied. The rational use of oral medication is recommended before application of other techniques of drug administration.

Adjuvant drugs may be used at any step to enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and to provide independent analgesic activity for specific types of pain.

3.2.1 WHO Analgesic Ladder - Step 1 for mild pain

The first step is the use of oral paracetamol, aspirin, or another non-steroidal anti-inflammatory drug (NSAID) for mild to moderate pain.

Paracetamol has minimal toxicity at recommended doses (up to 4 g per day), but may cause fatal hepatotoxicity and renal damage at higher doses.

NSAIDs are useful in bone pain, and some are available without prescription[40]. However, they carry a significant risk of serious and potentially fatal side-effects. Groups shown to be at high risk of gastrointestinal complications include the elderly (> 60 years of age), patients with a previous history of peptic ulcer, those receiving aspirin, oral steroids or anticoagulants[41]. If NSAID use cannot be avoided in these high-risk patients, gastroprotection in the form of misoprostol 200 µg four times daily[42] or omeprazole 20 mg once daily or famotidine 40 mg twice daily[43] should be given. Omeprazole at a daily dose of 40 mg is not more effective than at a dose of 20 mg daily[44].

The newer selective cyclooxygenase (COX) -2 inhibitors (coxibs) offer a reduced risk of gastrointestinal damage[45,46]. Such agents are associated with fewer serious adverse gastrointestinal reactions in average-risk patients in short term studies, but there is little published data in high risk

patients or chronic use. Coxibs have not been shown to protect against the renal and cardiovascular toxicity of NSAIDs. There are no published trials of COX-2 selective agents in cancer pain to date.

3.2.2 WHO Analgesic Ladder - Step 2 for mild to moderate pain

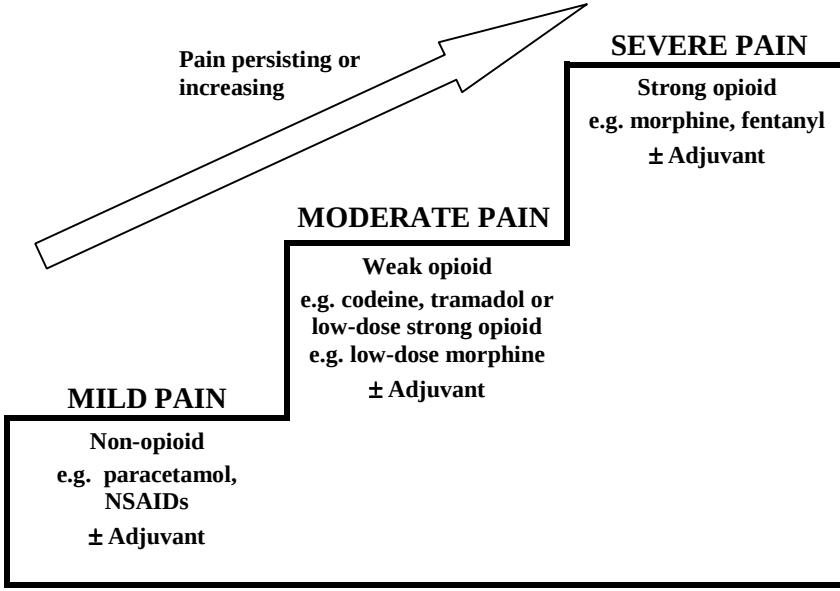
When pain persists or increases, a weak opioid, such as codeine or tramadol, should be added to the NSAID. The combination of opioid to paracetamol and/or an NSAID may minimise the dose of opioid required for effective analgesia[47].

Tramadol is an opioid with additional central effects on the monoaminergic system[48]. At therapeutic doses, its analgesic effects are similar to that of a non-opioid combined with an opioid for mild to moderate pain.

3.2.3 WHO Analgesic Ladder - Step 3 for moderate to severe pain

The third step is taken when pain is not completely relieved by a weak opioid in combination with NSAIDs. Weak opioids, such as codeine or tramadol, should be replaced with strong opioids such as morphine, fentanyl or methadone.

Figure 2 The WHO Analgesic Ladder for Cancer Pain Management



3.3 Use of Opioids in the treatment of moderate to severe pain

This section considers dosage, formulations, side effects and methods of administration of opioids.

B The opioid of first choice for moderate to severe pain is morphine.

Grade B, Level III

B The optimal route of administration is by mouth. There should ideally be two types of oral formulations: immediate-release for dose titration and controlled-release for maintenance treatment.

Grade B, Level III

B The opioid dose for each patient should be individually titrated to achieve maximum analgesia and minimum side effects.

Grade B, Level III

C Where possible, opioid dose titration should be carried out with an immediate-release morphine preparation given every four hours to maintain constant levels of analgesia.

Grade C, Level IV

A Once suitable pain control is achieved by use of immediate-release morphine, conversion to the same total daily dose of controlled-release morphine should be considered.

Grade A, Level Ib

C Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of immediate-release morphine. The breakthrough dose should approximate one-sixth of the total daily dose of oral morphine.

Grade C, Level IV

C If patients are unable to take opioids orally, the rectal, transdermal or subcutaneous route may be used. There is no indication for use of the intramuscular route for chronic cancer pain because the subcutaneous route is associated with less risk and less pain.

Grade C, Level IV

C The average relative potency ratio of oral to parenteral morphine is 1:3.

Grade C, Level IV

B A small proportion of patients develop intolerable side effects with oral morphine. In such patients a change to an alternative opioid or a change in the route of administration should be considered.

Grade B, Level III

A Transdermal fentanyl is an effective alternative to oral morphine, but is best reserved for patients with stable opioid requirements.

Grade A, Level Ib

C Methadone is an effective alternative drug, but is more difficult to use than other opioids because of pronounced inter- and intra-individual differences in its duration of action and relative analgesic potency. Its use by non-specialist practitioners is not recommended.

Grade C, Level IV

B Patients receiving opioid agonists should not be given a mixed agonist-antagonist because of the risk of precipitating a withdrawal syndrome and exacerbation of pain.

Grade B, Level IIb

B Pethidine should not be used if continued opioid use is anticipated.

Grade B, Level IIa

B Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia, or suffer intolerable side-effects, despite the optimal use of systemic opioids and non-opioids

Grade B, Level III

3.3.1 Principles of opioid use

The WHO Analgesic Ladder recommends that opioids be used in the second step (weak opioids) and third step (strong opioids) of the Ladder. The first principle of opioid use in cancer pain is appropriate drug selection. The choice of medication is based on the severity of the patient's pain. The opioid of first choice for moderate to severe pain is morphine.[49, 50]

Secondly, clinicians should be familiar with the availability of and indications for various routes of opioid administration. The oral route is preferred in chronic pain. The enteral route may be used in patients with nasogastric or percutaneous feeding tubes.

Oral immediate-release morphine sulphate is the first-line opioid treatment for moderate to severe cancer pain. A typical starting dose is 5-10 mg orally every four hours.

When pain is controlled, the same level of analgesia can be achieved by giving the total daily amount of immediate-release morphine as controlled-release morphine.

Orally administered morphine provides pain relief comparable to that of parenterally administered morphine if the "first pass" effect in the liver is taken into account. This is also the basis of the 3:1 oral-to-parenteral dose ratio.

Pain severity, age and previous use of weak opioids for mild to moderate pain should be considered when choosing the initial dose of opioid for moderate to severe pain. Extra care should be taken in patients with renal impairment. Apart from opioids which have a ceiling effect, e.g. codeine and buprenorphine, there is no predetermined maximum dose of an opioid. The appropriate dose is that which relieves pain without major side-effects. Periodic dose titration may be required because of the natural history of the disease or because of the development of tolerance. When changing the opioid or route of administration, adjustments should be made to correct for differences in drug potency.

3.3.2 Breakthrough analgesia

Breakthrough pain is defined as an increase in pain to greater than moderate intensity occurring on a baseline pain of moderate intensity or less[25]. One-sixth of the total daily morphine dose can be taken at any time for this[50].

3.3.3 Parenteral administration

Subcutaneous or intravenous administration may benefit patients who are unable to take opioids orally. Indications for parenteral opioids include inability to swallow, nausea and/or vomiting, gastrointestinal obstruction and impaired gastrointestinal absorption. Medications may be given as repeated intermittent bolus doses or by continuous infusion[51]. Intravenous injections provide almost immediate analgesia; subcutaneous doses may require up to 15 minutes for effect.

Subcutaneous continuous infusions of morphine are effective and may be used for prolonged periods of time. Such infusions can be administered at home, provided that the caregiver receives appropriate instruction[52]. The subcutaneous site should be inspected, and possibly rotated, every 48-72 hours. This is especially important in neutropenic patients in order to minimize the risk of site infection.

Intramuscular injections should be avoided because they are painful, inconvenient, and associated with erratic absorption.

3.3.4 Alternative opioids to morphine in moderate to severe cancer pain

Fentanyl is a semi-synthetic opioid. It is not used by mouth because of extensive first-pass metabolism. Its low molecular weight and high lipid solubility facilitate transdermal absorption. Transdermal fentanyl has been shown to have clinical efficacy in pain relief similar to that of morphine[53].

When using the fentanyl patch, the amount released per unit of time is proportional to the surface area of the patch in contact with the skin. The maximum recommended dose is 300 µg/hr. Patients requiring larger doses should be given opioids by alternative routes. The transdermally administered drug must first accumulate in depot sites subcutaneously before clinically relevant plasma drug levels can be achieved. Plasma levels rise slowly over 12-18 hours after transdermal patch placement, and taper off within 20-24 hours after patch removal. A transdermal system is therefore inappropriate for rapid dose titration and should only be considered in patients with relatively stable pain[54]. Constipation and nausea are generally less troublesome than with oral opioids, because the transdermal drug avoids the gastrointestinal tract[55]. The high cost of transdermal fentanyl should be considered before its chronic use.

Methadone is an effective analgesic[56]. Dose titration is difficult because of the wide degree of variation in drug half-life between individual patients, as well as variation in half-life occurring over time in individuals[57]. Specialist advice should be sought concerning dose conversion and titration.

3.3.5 Opioids NOT recommended for use in moderate to severe cancer pain

Agonist-antagonist opioids (e.g. buprenorphine) are not preferred for cancer pain management. They may precipitate a withdrawal reaction with worsening pain when administered to individuals concurrently receiving a pure agonist opioid. They should never be given simultaneously or alternated with pure opioid agonists, such as morphine or

fentanyl. Furthermore, agonist-antagonist opioids have a high incidence of ceiling and dysphoric effects[58-59].

Pethidine (Meperidine) has a short half-life. It also has a toxic metabolite (norpethidine) which may accumulate and cause seizures with chronic administration[60]. This is of particular importance in the elderly and in patients with abnormal renal function.

3.3.6 Specific issues regarding opioid use

A Specific interventions to treat the adverse effects of opioid therapy are efficacious.

Grade A, Level Ib

B Constipation is a common problem associated with long-term opioid administration and should be treated prophylactically.

Grade B, Level III

B When naloxone is given to reverse opioid-induced respiratory depression, it should be titrated to improve respiratory function, but with preservation of analgesia.

Grade B, Level IIb

C Mental clouding or confusion due to opioid toxicity should be managed by reducing the dose of opioid, ensuring adequate hydration and treating the agitation/confusion with a neuroleptic, such as haloperidol.

Grade C, Level IV

B Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence or addiction.

Grade B, Level III

B Patients prescribed opioids for pain should be reassured that they will not become psychologically dependent on or addicted to their opioid analgesia.

Grade B, Level III

3.3.6.1 Opioid side-effects

A minority of patients will experience excessive adverse side effects with the use of morphine and other potent opioids. The main approaches to the management of these effects include: dose reduction of systemic opioid, symptomatic management of the adverse effect(s), opioid rotation (or switching), and changing the route of administration[61]. The common opioid side-effects are constipation, nausea and vomiting, and sedation. Less common side effects include respiratory depression, confusion, myoclonus, pruritus and urinary retention.

Constipation
All patients on opioids should receive concurrent prophylaxis for constipation. A combination of softening (e.g. lactulose, liquid paraffin) and stimulant laxatives (e.g. senna, bisacodyl) is often required[62,63]. Tolerance to this side-effect does not develop with continued opioid use.

Nausea and vomiting
In clinical practice, 30% to 60% of opioid-naïve patients experience nausea and/or vomiting. Persistent nausea is rare. Tolerance to this side-effect occurs in the majority of patients within 5 to 10 days. Transient symptoms can be treated with standard antiemetic medications. Treatment of factors contributing to nausea (e.g. constipation) should be considered where appropriate.

Sedation
Sedation may be treated by eliminating contributing factors, such as non-essential drugs and metabolic disturbances, by reducing the dose of opioid by 25% to 50% if analgesia is satisfactory, or by adding an adjuvant analgesic to allow adequate pain relief on a lower dose of opioid. Other strategies include switching to another opioid, using stimulant drugs (e.g. methylphenidate 5-10 mg om) or considering other treatment modalities.

Respiratory depression
Respiratory depression is uncommon because pain serves as a stimulus to respiration. In established cases, the smallest possible amount of naloxone should be administered to preserve analgesia and to avoid withdrawal[63a]. A continuous naloxone infusion may be necessary because of its short half-life.

Mental clouding or Confusion
An opioid-induced confusional state is an indication that the dose of opioid should be reduced. The degree of dose reduction depends on whether other drugs or other pain-relieving modalities are used, the renal function, and the response of the pain to opioids. The addition of low-dose neuroleptic medication (e.g. haloperidol) may occasionally be necessary.

Myoclonus
This is benign and is not usually a clinical problem. Valproate or clonazepam may be administered if myoclonus disturbs sleep, impairs function or increases pain. A reduction in dose or change in opioid should be considered with severe or refractory myoclonus.

Pruritus
Pruritus is a rare problem with chronic opioid use. A trial of antihistamines should be considered if it occurs.

Urinary retention
Urinary retention may occasionally be associated with opioid use. Urinary catheterisation or treatment with a direct-acting cholinomimetic agent such as bethanecol may be necessary.

3.3.6.2 Addiction

Addiction is a psychological and behavioural syndrome characterized by loss of control over drug use and compulsive, continuous use despite harmful side effects. Persons addicted to opioids crave the psychic effects of these drugs, and exhibit drug-seeking behaviour. The treatment of cancer pain leads to addiction in well under 1% of patients who have no history of drug addiction[64]. In a large prospective study, only four cases of iatrogenic addiction could be identified among 11,882 patients with no history of addiction who had received opioids in the hospital setting[65].

Physical dependence is not the same as psychological addiction. The former refers to the pharmacological property of opioids that results in a withdrawal, or abstinence, syndrome when the drugs are abruptly discontinued. Withdrawal symptoms include rhinorrhoea, lacrimation, diarrhoea, anxiety, yawning, chills, hyperventilation, hyperthermia, muscle aches and vomiting[64]. This syndrome can be avoided by tapering of the opioid dose.

3.3.6.3 Tolerance

Tolerance to a drug is defined as the failure of a steady dose of the drug over time to sustain the desired pharmacological effect. The drug dosage then must be increased to maintain the original therapeutic goal. Clinically relevant pharmacological tolerance to opioid analgesia rarely occurs in chronic cancer pain management. Cancer patients with stable disease seldom escalate their opioid dose; this usually occurs in the setting of recurrent or progressive cancer[66].

3.4 Adjuvant drugs

Adjuvant drugs are those which are not classified primarily as analgesics, but which are useful in certain painful conditions[67].

A Patients with neuropathic pain should have a trial of a tricyclic antidepressant and/or an anticonvulsant.

Grade A, Level Ia and Ib

C A trial of steroids should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, and spinal cord compression.

Grade C, Level IV

3.4.1 Tricyclic antidepressants (TCAs)

TCAs include amitriptyline, imipramine, desipramine and nortriptyline. They are effective in relieving neuropathic pain[47]. The antineuralgic properties of TCAs are independent of their antidepressant properties. There are no significant differences in efficacy between the different tricyclic antidepressants. The doses required are generally lower than those used to treat clinical depression.

3.4.2 Anticonvulsants

Carbamazepine, phenytoin, sodium valproate and gabapentin have been widely used to treat neuropathic pain of non-malignant aetiology[47,68].

When used for neuropathic pain, there is no significant difference between tricyclic antidepressants and anticonvulsants with respect to analgesic benefit, or the risk of adverse events[47].

3.4.3 Steroids

There is some evidence for the usefulness of steroids in treatment of cancer pain. Clinical experience indicates that steroids can be useful in malignant spinal cord compression[69], raised intracranial pressure, severe bone pain, as well as pain from pressure due to soft tissue swelling or infiltration. Dexamethasone in doses up to 24 mg per 24

hours, intravenous or oral, may be required. The dose and duration of treatment depend on the clinical response.

3.4.4 Antiarrythmic agents

Lignocaine[70] (given as a parenteral infusion) and its oral congener, mexiletine[71], have been successfully used to treat neuropathic pain. Response to intravenous lignocaine predicts subsequent response to oral mexiletine. Use of these agents should be supervised by specialists who are familiar with their use.

3.4.5 Ketamine

Ketamine is an anaesthetic agent which is a non-competitive blocker of the N-methyl-D-aspartate (NMDA) receptor. It has been used parenterally[72] and orally[73] to treat neuropathic pain which has not responded to a combination of opioids and other adjuvant agents. It has significant psychomimetic adverse effects. Advice should be sought from specialists familiar with its use.

3.5 Bisphosphonates and Calcitonin

A Bisphosphonate treatment should be considered for all patients with multiple myeloma and breast cancer patients who have pain due to metastatic bone disease, in addition to conventional analgesic techniques.

Grade A, Level Ia and Ib

Bisphosphonates should be considered where analgesia and/or radiotherapy are inadequate to manage painful bone metastases. There is insufficient evidence to recommend bisphosphonates for relief of acute pain, or as first line therapy.

There is evidence to support their role in a long-term strategy to reduce pain from bone metastases: the evidence is best for multiple myeloma[74] and breast cancer[75,76], and less robust in other malignancies[77,78]. The bisphosphonates demonstrated to be effective in reduction of bone pain are pamidronate and clodronate. With both drugs, intravenous therapy is better tolerated and more effective than oral therapy.

Calcitonin is a potent inhibitor of osteoclast-induced bone resorption and, like the bisphosphonates, is used in the management of hypercalcaemia of malignancy. There is some evidence to suggest that it helps to reduce the pain of bone metastases[79].

C Systemic chemotherapy should be considered for cancers which are highly chemosensitive.

Grade C, Level IV

C Hormonal manipulation may contribute to pain relief in hormone sensitive cancers.

Grade C, Level IV

C Radiotherapy is effective in relieving pain due to tumour infiltration.

Grade C, Level IV

C When using anti-tumour therapy, concomitant use of effective analgesics must not be neglected.

Grade C, Level IV

Modalities which reduce tumour load either locally or systemically have a role in cancer pain relief in conjunction with conventional analgesics. Factors to be taken into account include their therapeutic efficacy, potential toxicity and the effect on quality of life.

4.1 Chemotherapy

Systemic chemotherapy should always be considered in patients with highly chemosensitive cancers, such as breast cancer[80], small cell lung cancer[81], pancreatic cancer[82], malignant lymphoma, acute leukaemia and myeloma, ovarian cancer and germ cell cancer.

Whenever possible, a single agent should be used instead of a complex schedule of combination chemotherapy.

The effect of chemotherapy is temporary and usually not complete. Pain will return as soon as tumour resistance develops and the tumour progresses. It is important to continue the use of effective analgesics[83].

4.2 Endocrine therapy

Hormonal manipulation can lead to regression of hormone-sensitive tumours, and provide pain relief. It should be considered in patients with cancers, such as hormone receptor positive breast cancer and prostate cancer.

The response to endocrine therapy is usually slower than to systemic chemotherapy. Concomitant use of effective analgesics must not be neglected.

4.3 Radiotherapy

Radiotherapy can relieve pain due to local tumour infiltration, as in skeletal and cerebral metastases[84], spinal cord compression[85], and lymphadenopathy,

When radiotherapy is given to relieve pain, rather than with curative intent, a small fraction number and low total dose should be used.

Radiopharmaceuticals such as strontium-89 have been shown to be as effective as external beam radiation for patients with metastatic prostate cancer[86, 87].

Table 5 Examples of chemotherapy and hormonal therapy

Cancer Type	Chemotherapy	Indication	Grades of recommendation and levels of evidence
Lymphoma	Combination or single agent chemotherapy e.g. Cyclophosphamide/ doxorubicin/ vincristine/ prednisolone (CHOP)	Pain associated with tumour infiltration	Grade B, Level III
Breast cancer	Combination or single agent chemotherapy e.g. Cyclophosphamide/ methotrexate/ 5-fluorouracil (CMF), Doxorubicin/ cyclophosphamide (AC)	Pain associated with fungating ulcer, hepatomegaly	Grade C, Level IV
Small cell lung cancer	Etoposide/cisplatin (EP)	Pain associated with tumour infiltration	Grade C, Level IV
Ovarian cancer	Paclitaxel/ carboplatin	Pain due to carcinomatosis peritonei	Grade C, Level IV
Pancreatic cancer	Combination or single agent chemotherapy e.g. Gemcitabine	Pain associated with para-aortic lymphadenopathy	Grade A, Level Ib
Prostate cancer	LHRH-agonist e.g. leuprolide acetate or goserelin acetate	Pain associated with bone metastases	Grade B, Level III

4 Interventional Techniques

C Professionals who manage patients with cancer pain should be aware of the range of interventional techniques available for the relief of pain and have access to a specialist pain clinic providing a range of interventional techniques.

Grade C, Level IV

GPP Non-invasive therapies should always precede invasive treatments, except in rare instances.

GPP

A Coeliac plexus block should be considered in patients with upper abdominal pain, especially when secondary to pancreatic cancer.

Grade A, Level Ia and Ib

A Epidural, intrathecal and intraventricular opioids should be considered in treatment of cancer pain not controlled with opioids by other routes.

Grade A, Level Ia and Ib

The role of interventional pain-relieving modalities in cancer pain management is not well defined. These techniques may provide alternative methods of long-term pain relief for patients when pain is not well controlled by simpler methods, such as systemic drug therapy or physical and psychological therapy. They can also be used for short-term analgesia for patients with severe acute pain, or in other situations where more definitive treatment is anticipated.

Non-invasive analgesic approaches should almost always precede invasive palliative modalities. Before invasive therapy is considered, the risk-benefit ratio, availability of expertise and suitable support systems and cost should be considered in addition to the medical indications. As in other areas of pain medicine, a multidisciplinary approach is helpful.

The low levels of evidence for the effectiveness of some of these treatments are often due to difficulties in performing randomised controlled trials in this field, rather than to the ineffectiveness of the interventional therapies concerned.

Interventional techniques for pain relief should only be considered in the following circumstances:

1. When standard treatments such as systemic drug therapy (oral, transdermal, subcutaneous etc.), behavioural and physical therapy fail to produce sufficient pain relief or are associated with unacceptable side effects.
2. After evaluation of the psychological and social circumstances.
3. After exclusion of other causes for incomplete analgesia.
4. When the patient is medically fit for the procedure.
5. After obtaining informed consent
6. Where there is a reasonably high probability of a good therapeutic response.
7. When expertise in performing the procedure is available.
8. Where there are adequate support services.

5.1 Neural blockade

Neural blockade usually involves the application of local anaesthetic and/or neurolytic agent to a peripheral nerve, nerve plexus (somatic, visceral or sympathetic), or central neural structure to block neural pain transmission. Apart from therapeutic indications, nerve blocks can be performed for diagnostic and prognostic purposes.

Administration of local anaesthetics, such as lignocaine, bupivacaine, levobupivacaine and ropivacaine, will cause temporary, reversible neural blockade. It is useful for acute pain relief while awaiting definitive treatment, provision of diagnostic information (e.g. whether the pain arises from the somatic or visceral neural pathway; whether a sympathetic mechanism is involved) and prognostic information (e.g. to assess the potential success or side effects that may result from a planned neurodestructive procedure). Catheters can also be placed at various sites to allow local anaesthetic infusions for more prolonged pain relief.

Injection of a neurolytic agent such as alcohol or phenol leads to nerve destruction and more prolonged neural blockade. Neurolytic blockade is usually performed after test injection of local anaesthetic has been shown to produce pain relief. Alcohol is the most common neurodestructive agent used in Singapore.

Neurolytic sympathetic blockade is especially useful in relieving pain in the arm, head and neck (stellate ganglion block), or leg (lumbar sympathetic block), as well as to interrupt the visceral afferent pain pathways mediating pain from the pancreas and other upper abdominal organs (coeliac plexus block) or in the pelvis (superior or inferior hypogastric block).

Coeliac plexus block is useful in managing intractable pain secondary to upper abdominal malignancies[88-91]. Four-fifths or more of patients with pancreatic or other abdominal cancers derive pain relief from coeliac block, usually lasting until death supervenes[91-92]. Even when pain relief is incomplete, patients may benefit from the lowering of their opioid dosage, with concomitant reduction in opioid side effects. Early coeliac neurolytic block should be considered for patients with pain from pancreatic cancer who have a short life expectancy[91].

The side effects of coeliac block include transient hypotension and diarrhoea. Known complications are paraplegia (rare with radiological guidance), radicular weakness or numbness, intrarenal injection and damage, retroperitoneal haematoma, and ejaculatory failure[88,93].

In contrast, neurolytic blockade of peripheral nerves (e.g. intercostal neurolytic block for chest wall pain) should be attempted only in patients with short prognoses, because of the high incidence of post-procedure neuralgic pain. Pain recurrence occurs because the alcohol-damaged nerve regenerates over weeks to months.

After a successful interventional procedure, patients already on opioids should have the dose reduced by approximately one-third to avoid acute respiratory depression. If a patient is pain free after the interventional procedure, opioids should not be stopped abruptly, so as to avoid precipitating opioid withdrawal syndrome.

Table 6 Examples of Neurolytic Blocks

Sites	Procedure	Indications	Grades of recommendations and levels of evidence
Central			
Subarachnoid (intrathecal) neurolytic block	Blocks the dorsal (sensory) nerve roots of spinal nerves within the spinal canal	Intractable, unilateral, somatic pain over the thoraco-abdominal region encompassing a few dermatomes[94,95]	Grade C, Level IV
Visceral sympathetic blocks			
Coeliac plexus block	Blocks the sympathetic / sensory innervation of the upper abdominal viscera	Pain secondary to malignancies of the upper abdomen and retroperitoneum (especially pancreatic cancers)	Grade A, Level Ia and Ib
Superior hypogastric plexus block	Blocks the sympathetic / sensory innervation of the pelvic viscera	Intractable pelvic pain secondary to malignancies of the cervix, prostate and other pelvic viscera. [96,97]	Grade C, Level IV
Peripheral nerve blocks			
Trigeminal ganglion block	Peripheral neurolysis of the trigeminal ganglion and its branches	Intractable pain secondary to head and neck malignancies[98,99]	Grade C, Level IV
Intercostal neurolytic blocks	Neurolysis of intercostal nerves	Intractable chest wall pain	Grade C, Level IV

5.2 Epidural and intrathecal drug delivery systems

In selected patients, intraspinal (epidural or intrathecal) opioid infusion via catheter systems inserted at the appropriate level of the spinal cord may be utilised to produce profound analgesia without motor, sensory, or sympathetic blockade[100-102]. This is often achievable with relatively low opioid doses and fewer side effects, because intraspinal opioids directly activate opioid receptors in the spinal cord[103,104]. These systems are ideal for difficult abdominal or pelvic pain, and diffuse pain not amenable to regional interventional therapy. Local anaesthetics and $\alpha 2$ adrenergic agonists such as clonidine given intraspinally act to potentiate the effect of opioids, and are safe and effective[105,106].

For short-term use, epidural catheters can be placed percutaneously and fixed either by secure taping or subcutaneous tunnelling. The drugs are delivered through a portable pump or a syringe driver. Patients may be ambulant and managed as outpatients with these systems.

In patients with a longer life expectancy, fully implantable intrathecal systems offer greater freedom because there is no external equipment, and the drug reservoir only needs refilling every few weeks. Some pumps are programmable and offer greater flexibility. However, the cost of programmable systems may be prohibitive, and patients require close follow-up by the managing clinicians.

5.3 Neurosurgical techniques

Neurosurgical techniques have a small place in the multimodal approach to pain management.

Cordotomy is used to treat pain on one side of the body. It may be performed as an open operation or as a percutaneous procedure. An example is percutaneous cordotomy at the cervical C1-2 region, which provides analgesia up to about the C4 level, which corresponds to the shoulder. Complete analgesia can be achieved in this manner in about two-thirds of patients[107].

Other neurosurgical procedures include placement of an Omaya reservoir or catheter into the ventricular system to deliver analgesics. This is particularly useful for facial and head pain[102].

C Cutaneous stimulation techniques, such as application of superficial heat and cold as well as massage, pressure and vibration, may provide pain relief when the source of pain is associated with muscle tension or spasm.

Grade C, Level IV

A Patients should remain active and participate in self-care when possible.

Grade A, Level Ib

B Prolonged bed-rest for cancer patients should be avoided because prolonged immobilization may lead to joint contractures, muscle atrophy, cardiovascular deconditioning, and other undesirable effects.

Grade B, Level III

A Psychosocial interventions should be used concurrently with pharmacological treatment for pain as part of a multidisciplinary approach to pain management and not as substitutes for analgesics.

Grade A, Level Ib

B Education on effective pain control modalities and correction of misconceptions relating to the use of opioids should be a routine part of patient management.

Grade B, Level III

GPP Pastoral care team members should participate in health care team meetings that discuss the needs and treatment of patients. They should be conversant with community resources that provide spiritual care and support for patients and their families.

GPP

Physical and psychosocial therapies are an integral part of the multimodal approach to pain management. They should be used concurrently with pharmacological and other treatment modalities. Such interventions can be carried out either by professional staff or by the patient and caregivers.

6.1 Physical therapies

Physical therapies include cutaneous stimulation, immobilization, exercise, transcutaneous electrical nerve stimulation (TENS), and acupuncture[108]. The use of these modalities may reduce the need for analgesic drugs, but they should not be used as substitutes for medication. They should be introduced early to prevent generalized weakness and deconditioning, as well as to treat aches and pains associated with periods of inactivity and immobility related to cancer and its therapy.

6.1.1 Cutaneous stimulation

This includes the application of superficial heat (thermotherapy) and cold (cryotherapy)[109]. Other methods, such as massage, pressure, and vibration, may help patients to relax, or to distract them from their pain. Cutaneous stimulation sometimes increases pain briefly before pain relief occurs[110]. These methods are non-invasive and usually can be easily taught to the patient or family caregiver.

6.1.2 Exercise

Exercise is important for the treatment of subacute and chronic pain because it strengthens weak muscles, mobilizes stiff joints, helps restore coordination and balance, enhances patient comfort, and provides cardiovascular conditioning[111-114]. Some patients may use position change or exercise as a self-initiated strategy for pain relief; of those who used these strategies, 86% reported pain relief with change of position and 25% reported pain relief after exercise[113]. Patients should be encouraged to remain active and participate in self-care when possible. Prolonged bed-rest for cancer patients should be avoided because prolonged immobilization may lead to joint contractures, muscle atrophy, cardiovascular deconditioning, and other undesirable effects[114].

6.1.3 Counter-stimulation

Counter-stimulation denotes techniques, such as TENS therapy and acupuncture, that are believed to activate endogenous pain-modulating pathways by direct stimulation of peripheral nerves. The literature in support of these

interventions is inconclusive, although some patients report relief from their use[115, 116].

6.2 Psychosocial Interventions

Psychological forces are important in pain perception. Psychosocial interventions can help patients gain a sense of control over their pain by changing their sensitivity, feelings and reactions[117]. They should be introduced early in the course of illness so that patients can learn and practice these strategies while they have sufficient strength and energy. Patients and their caregivers should be taught strategies commonly used to manage pain and anxiety, encouraged to try different ones, and to select one or more to use regularly as required.

Cognitive and/or behavioural techniques may be employed. Cognitive techniques focus on perception and thought patterns. They are intended to influence how one interprets events and bodily sensations. Providing patients with information about their pain and its management and helping patients to think differently about their pain are examples of cognitive techniques. Behavioural techniques are directed at helping patients develop skills to cope with pain and to modify their reactions to pain.

Peer support groups bring together people who are grappling with common concerns and challenges of cancer and provide an environment where they can share information, experiences, coping strategies and feelings. They may be helpful to individuals without an adequate network of social support.

7 Pain in Special Populations

B Clinicians should give special attention to the assessment and treatment of pain in special populations, including the very young, the very old, the cognitively impaired, and known or suspected substance abusers. Aggressive pain assessment and management are as necessary for them as for the general population.

Grade B, Level III

B Behavioural observation should be the primary assessment method for preverbal and nonverbal children, and used as an adjunct for assessment of verbal children.

Grade B, Level III

B In older children, assessment includes self-report using age-appropriate scales, such as the Faces Pain Scale, and the Numeric Rating Scale. Observation should be used as an adjunct to self-reported pain.

Grade B, Level IIb

C Oral medication in children with cancer pain should follow the WHO analgesic ladder, with dosage adjustments. The basic principles of opioid use are similar to those in adults.

Grade C, Level IV

GPP Assessment in the cognitively intact elderly patient with cancer pain should be done in ways similar to that of the general adult population.

GPP

B Behavioural observation should be an adjunct to cancer pain assessment in cognitively impaired adults.

Grade B, Level, III

C Non-opioid analgesic modalities should not be substituted for opioid analgesics to treat severe pain in the suspected or known substance abuser.

Grade C, Level IV

7.1 Pain in Children

Pain is common in children with cancer, with an incidence between 25% to 50%[118-120]. Treatment-associated pain accounts for more than half of this, with only about a quarter attributable to the cancer itself. Procedure-related pain and anxiety are important sources of discomfort in the paediatric cancer patient[120]. Child-specific interventions are associated with improved analgesia and health outcomes[121]. Special consideration should be given to the following factors when dealing with children[122, 123]:

1. Dose adjustment of medications to suitable levels:
2. Minimization of procedure-related pain and anxiety by considering less invasive procedures, pre-medication (e.g. with topical anaesthetics) and aggressive management of treatment-associated morbidity (e.g. mucositis).
3. Childhood behavioural norms. Assessment and management strategies should be tailored to the child's developmental level, as well as to existing emotional and physical resources. This is especially necessary in children with developmental delay, learning handicaps or emotional disturbances
4. A high index of suspicion should be maintained in the assessment of pain in children.

7.1.1 Pain assessment in children

The Visual Analogue Scale, McGill Pain Questionnaire[31], Faces scale[33,34], Poker Chip tool[124,125], and drawings[126] are recommended assessment tools for children with no cognitive impairment and who are old enough to understand the tools. No validated tools are available in the English language for children with cognitive impairment, children unable to communicate because of their age and poor physical status, and younger children less than 2 years old.

Development of behaviour associated with chronic pain, such as apathy and depression rather than overt crying or struggling, can occur after only a few days of continuing severe pain. A trial of analgesics can be diagnostic as well as therapeutic, if there is uncertainty as to the relationship of a child's behaviour to existing pain.

7.1.2 Pain treatment in children

The starting dose for oral and parenteral morphine in children is 0.3 mg/kg every 4 hours and 0.1 mg/kg every 4 hours, respectively. The initial dose must be reduced by 1/4 to 1/3 in babies less than 6 months of age because of increased elimination half-life and increased blood-brain barrier permeability in infants[127]. If the child is not being ventilated, there should be close monitoring, as there is increased risk of respiratory depression and opioid-induced sedation.

Liquids or suspensions should be employed whenever possible. Repetitive exposure to needles should be minimised. Parenteral patient-controlled analgesia can be used with older children.

7.2 Pain in the elderly

Elderly patients are often undertreated for their pain[128] because of:

1. Inappropriate beliefs about pain tolerance and sensitivity
2. Fear of drug-related adverse events
3. Difficulty in pain assessment, especially in the cognitively impaired and in those with sensory handicaps (e.g. the hearing-impaired).
4. Failure of the older individual to report pain. Some may expect pain to be an inevitable part of the disease process, or of aging. Others may be apprehensive over the consequences of reporting pain (e.g. being considered a nuisance) or of the implications of pain (advancing disease, further interventions or hospitalisation).

The patient's self-report is the most accurate and reliable evidence of the existence or intensity of pain.

Elderly patients are subject to greater risk of adverse drug reactions because of:

1. age-related changes in pharmacokinetics resulting in decreased drug clearance;
2. increased central nervous system sensitivity to medications such as opioids;
3. a higher incidence of concurrent illnesses, with higher risks of drug-disease interaction.

Starting doses may need to be lowered, and dose titration should be carried out more cautiously in the elderly[128]. A typical starting dose of oral morphine for the opioid-naïve frail, elderly person would be 2.5 mg three times a day.

7.3 Adults with cognitive impairment

No valid instrument is presently available for the assessment of pain in this group of patients. Some working groups recommend the use of the standard 4-point verbal rating scale of no, mild, moderate or severe pain[130].

7.4 Adults who are unable to communicate

Observer rating with the use of the 4-point verbal rating scale[130] may be used. In the verbally communicative cognitively impaired elderly, the evidence suggests that even moderately to severely demented patients are able to reliably report pain felt at the time of assessment, although pain recall in integration of pain experience over time may be less reliable[131, 132].

7.5 Pain in substance abusers

Current and previous substance abusers are at increased risk of undertreatment of pain. Management problems with opioid use can be classified into:

1. Tolerance - Previous opioid abusers would have a higher degree of opioid tolerance than the general population. This decreases the duration of effective analgesia, with a need for more frequent dosing to achieve adequate pain relief.
2. "Pseudo-addiction" - Inadequate analgesia for pain, possibly as a consequence of fear of opioid diversion or "true" addiction, leads to inadequate pain relief and phenomena consisting of clock-watching, manipulative behaviour, and demands for opioids. This behaviour resolves when the pain is effectively treated.
3. Addiction - This is manifested by loss of control, compulsive use, continued use despite harm, a failure to set limits and drug craving[133]. Suspicion of addiction should be raised when there is inability to take medications according to an agreed-upon schedule, taking of multiple doses together, frequent reports of lost or stolen prescriptions, doctor-hopping, isolation from family and friends, and/or use of non-prescribed psychoactive drugs in addition to prescribed medications. Other behaviours which may

raise concern are the use of analgesic medications for other than analgesic effects, such as sedation, an increase in energy, a decrease in anxiety, or intoxication; non-compliance with recommended non-opioid treatments or evaluations; insistence on rapid-onset formulations/routes of administration; and reports of no relief whatsoever by non-opioid treatments.

Where patients exhibit behaviour suggestive of addiction[134]:

1. A psychiatrist should be a part of the clinical team to manage psychological problems such as depression, anxiety and personality disorder.
2 Expectations and limits of acceptable and unacceptable behaviour should be discussed. These include:
   - Setting restrictions on breakthrough doses (if medication is given orally) and "lock-out" periods (if parenteral patient-controlled analgesia is used).
   - Witnessed administration and routine searches (if the patient is an in-patient)
   - Prescription renewals by only one designated clinician.
   - Reporting of forgery and theft of prescriptions.
3 Long-acting opioid preparations are preferred over short-acting preparations.

7.6 Pain in patients with Acquired Immune Deficiency Syndrome (AIDS)

Patients with AIDS often have pain problems similar to those with cancer. Recommendations for pain assessment and management in these guidelines are generally applicable to pain in patients with HIV.

The prevalence of pain in HIV-infected individuals varies depending on the stage of disease. It ranges from 40% to 60%, with increasing prevalence as the disease progresses[135].

Use of adjuvants together with opioids is important in treatment of neuropathic pain[136, 137].

Zidovudine and paracetamol may be used together but may interact significantly.

Common pain syndromes associated with the HIV-infected patient include[138]:

- Painful sensory neuropathy as a result of HIV infection or treatment (e.g. with didanosine, zalcitabine, isoniazid, vincristine)
- Post-herpetic neuralgia
- Arthritis (Reiter's syndrome, reactive arthritis, psoriatic arthropathy, septic arthritis) and myalgia (polymyositis and muscle spasticity from encephalopathy)
- Abdominal pain (intestinal infections with *Mycobacterium avium-intracellulare* and cryptosporidium, hepatosplenomegaly)
- Odynophagia (oesophageal candidiasis)
- Headache (HIV encephalitis, toxoplasmosis, AZT-induced)

Psychological morbidity is high in patients with HIV, requiring special vigilance and management.

8 Education on Cancer Pain

Barriers that can account for suboptimal pain management[139-143] include:

Health Professional Factors

1. Lack of education on pain assessment and treatment
2. Belief that patients are poor judges of the severity of their pain
3. Inadequate knowledge of the distinction between tolerance, physical dependence and psychological dependence (addiction)
4. Belief that only "terminal" patients should receive opioids
5. Excessive fear of analgesic-induced toxicity
6. Excessive fear of using controlled drugs
7. Inadequate use of a multimodal approach to therapy

Patient and Family Factors

1. Lack of awareness that pain can be treated, and the best way to obtain access to effective therapy
2. Under-reporting of pain for fear of acknowledging progression of disease and concern about distracting physicians from treatment of the underlying disease
3. Fear of addiction to drugs
4. Fear of side-effects of drugs
5. Fear of developing tolerance to drugs
6. Cultural or religious influences that cause them to value suffering
7. A perception that opioids are only for dying patients

Teaching curricula for health care professionals must therefore address these factors so as to prepare them to effectively assess and manage cancer pain. Clinicians managing pain should provide education about pain and its management to cancer patients and their families as part of the treatment plan. Patients should be encouraged to be active participants in pain management by giving both verbal and written information to their caregivers.

9 Quality Indicators in Cancer Pain Management

9.1 System indicators

Health care system factors can result in poor cancer pain management. These include a lack of emphasis on cancer pain treatment and fragmentation of care among the numerous health care specialists caring for cancer patients.

The successful implementation of these guidelines will require institutional support, a willingness to collaborate across clinical and paraclinical disciplines as well as administrative coordination of hospital services.

- Formal means should be developed within each institution to evaluate cancer pain management practices.
- There should be clear lines of responsibility in cancer pain management as well as in its institutional evaluation
- Patients should have ready access to a specialist in pain relief, a palliative medicine specialist and/or an anaesthetist, depending on their clinical needs.

9.2 Process indicators

The key items that need systematic assessment in a pain management evaluation programme are the severity and progress of cancer-related pain, the accuracy of diagnostic procedures and the appropriate use of and referral for specialised analgesic techniques[144-146].

- All patients should be assessed for pain at points of transition in care (e.g. hospital to home, home to hospice)
- Information from the initial pain assessment and at follow-up visits, the proposed management and the pain scale adopted should be clearly documented.
- Regular reviews of pain management should be made with a view to optimization of current pain therapy and further referral to more specialised services if appropriate.
- Standard procedures should be established regarding use of specialised analgesic techniques. The procedures should define appropriate acceptable level of patient monitoring as well as appropriate roles and limits of practice for the health care provider.

9.3 Outcome indicators

Satisfactory pain control has a positive impact on quality of life and functional outcomes.

- Pain intensity scores and satisfaction with pain management are key outcome indicators in the management of cancer pain.

References

1. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer. 1982 Nov 1;50(9):1913-8.

2. Ho RCS. Pain in the cancer patient. (Editorial) CA Cancer J Clin 1994;44(5):259-61

3. Bonica JJ. Cancer pain. In: Bonica JJ, editor. The management of pain. 2nd ed. Vol. 1. Philadelphia: Lea and Febiger; 1990. p.400-60.

4. Coyle N, Adelhardt J, Foley KM, Portenoy RK. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. J Pain Symptom Manage 1990;5(2):83-93.

5. Chow P, Wong M, Foo KT. Clinical profile of stage D carcinoma of the prostate-a ten-year experience. Ann Acad Med Singapore 1993 Mar;22(2):254-6.

6. Lim TC, Teh LB, Kwok KC, Ng HS, Ong YY, Seah CS. Hepatocellular carcinoma--a clinical study. Ann Acad Med Singapore 1986 Apr;15(2):158-61.

7. Wang TL, Yap IL, Tan YO. Hepatocellular carcinoma--a case series of 104 patients. Ann Acad Med Singapore 1991 Mar;20(2):215-8.

8. FJ Jayaratnam, FL Sin, Nadarajah K, VP Yong et al. Pain in terminal cancer: its incidence and treatment in a general hospital. Sing Med J 1988; 29:557-564.

9. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with mestastic cancer.N Engl J Med 1994;330(9):592-6 (ECOG)

10. Addington-Hall J, McCarthy M. Dying from cancer: results of a national population-based investigation. Palliat Med. 1995 Oct; 9(4):295-305

11. Miser AW, Dothage JA, Wesley RA, Miser JS. The prevalence of pain in a pediatric and young adult cancer population. Clin J Pain 1987; 29(1):73-83.

12. Tay WK, Shaw RJ, Goh CR. A survey of symptoms in hospice patients in Singapore. Ann Acad Med Singapore 1994 Mar;23(2):191-6.

13. Foley KM. Pain relief into practice: rhetoric without reform. J Clin Oncol 1995;13(9):2149-51.

14. Ferrell BR, Rhiner M, Cohen MZ, Grant M. Pain as a metaphor for illness. Part I: Impact of cancer pain on family caregivers. Oncol Nurs Forum 1991; 18(8):1303-9.

15. Moinpour CM, Chapman CR. Pain management and quality of life in cancer patients. In: Lehmann RKA, Zech D, editors. Transdermal fentanyl: a new approach to prolonged pain control. Berlin: Springer-Verlag; 1991. p. 42-63.

16. Goisis A, Gorini M, Ratti R, Luliri P. Application of a WHO protocol on medical therapy for oncologic pain in an internal medicine hospital. Tumori. 1989 Oct 31;75(5):470-2.

17. Schug SA, Zech D, Dörr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symptom Manage 1990; 5(1):27-32.

18. Teoh N, Stjernsward J. WHO cancer pain relief program -- ten years on. Seattle: International Association for the Study of Pain, IASP Newsletter 1992; p.5-6.

19. WHO: Cancer pain relief and palliative care: Report of a WHO expert committee. Geneva, World Health Organization, 1990 (technical report series, no. 804.)

20. Ventafridda V, Caraceni A, Gamba A. Field-testing of the WHO Guidelines for Cancer Pain Relief: summary report of demonstration projects. In: Foley KM, Bonica JJ, Ventafridda V, editors. Proceedings of the Second International Congress on Pain. Vol. 16. Advances in pain research and therapy. New York: Raven Press, Ltd.; 1990. p. 451-64.

21. Grond S, Zech D, Schug SA, Lynch J, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. J Pain Symptom Manage 1991; 6(7):411-22.

22. Thomas EM, Weiss SM. Nonpharmacological interventions with chronic cancer pain in adults. Cancer Control 2000 Mar-Apr;7(2):157-64.

23. Kovner F, Spigel S, Rider I, Otremsky I, Ron I, Shohat E, Rabey JM, Avram J, Merimsky O, Wigler N, Chaitchik S, Inbar M. Radiation therapy of metastatic spinal cord compression. Multidisciplinary team diagnosis and treatment. J Neurooncol 1999 Mar;42(1):85-92.

24. Grossman, S.A., et al., Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage, 1991. 6(2): p. 53-57.

25. Foley KM., Pain assessment and cancer pain syndromes. In: Doyle D, Hanks GW, MacDonald N (editors). The Oxford Textbook of Palliative Medicine, 2nd edition. Oxford: Oxford Medical Publications, 1998. p. 310-331.

26. Von Roenn, J.H., et al., Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. Ann Intern Med, 1993. 119(2): p. 121-126.

27. Morgan AE., Lindley CM., Berry JI., Assessment of pain and patterns of analgesic use in hospice patients. Am J Hosp Palliat Care, 1994. 11: p. 13-9, 22-25.

28. American Pain Society Quality of Care Committee, Quality improvement guidelines for the treatment of acute pain and cancer pain. American Pain Society Quality of Care Committee [see comments]. JAMA, 1995. 274(23): p. 1874-1880.

29. Twycross R., Lack SA., Symptom Control in Advanced Cancer. 2nd edition. London: Pitman Books Ltd, 1984.

30. Fishman, B., et al., The Memorial Pain Assessment Card. A valid instrument for the evaluation of cancer pain. Cancer, 1987. 60(5): p. 1151-1158.

31. Daut, R.L., C.S. Cleeland, and R.C. Flanery, Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain, 1983. 17(2): p. 197-210.

32. Caraceni A., et al., Pain Measurement Tools and Methods in Clinical Research in Palliative Care: Recommendations of an Expert Working Group of the European Association of Palliative Care. J. of Pain and Symptom Management, 2002. 23(3): p. 239-255.

33. Melzack R., The McGill Pain Questionnaire in: R Melzack (Ed) Pain Measurement and Assessment. Raven Press: New York, 1993. p. 41-48.

34. Serlin, R.C., et al., When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain, 1995. 61(2): p. 277-284.

35. Hicks CL., Von Baeyer CL., Spafford PA., von Korlaar I., Goodenough B., The Faces Pain scale – revised: toward a common metric in paediatric pain measurement. Pain, 2001. 93: p. 173-183.

36. Bieri D., Reeve RA., Champion GD., et al., The Faces Pain scale for the self-assessment of pain experienced by children. Pain, 1990. 41: p. 139-150.

37. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer 1987; 59: 850-6.

38. Zech DF, Grond S, Lynch J, et al. Validation of the World Health Organisation Guidelines for cancer pain relief : A 10 year prospective study. Pain 1995; 63: 65-76.

39. WHO. Cancer pain relief and palliative care. Geneva: WHO, 1996.

40. Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers TC. Efficacy and safety of non-steroidal anti-inflammatory drugs for cancer pain : a meta-analysis. J Clin Oncol 1994; 12: 2756-65.

41. Hawkins C, Hanks G. The gastroduodenal toxicity of non-steroidal anti-inflammatory drugs. A review of the literature. J Pain Sympt Manag 2000; 20(2): 140-151.

42. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multi-centre, double-blind, placebo-controlled trial. Lancet 1988; 2: 1277-80.

43. Wu CS, Wang SH, Chen PC, Wu VC. Does famotidine have similar efficacy to misoprostol in the treatment of non-steroidal anti-inflammatory drug-induced gastropathy? Int J Clin Pract 1998 Oct;52(7):472-4.

44. Hawker CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338: 727-34.

45. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343: 1520-8.

46. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomized controlled trials. BMJ Sept 2002; 325: 619-623

47. McQuay H, Moore A. Bibliography and systematic reviews in cancer pain. A report to the NHS National Cancer Research and Development Programme. Oxford 1997.

48. Tramadol – a new analgesic. Drug The Bull. 1994; 32: 85-7.

49. Morphine in cancer pain: modes of administration. Expert Working Group of the European Association of Palliative Care. BMJ 1996; 312: 823-6.

50. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Expert Working Group of the Research Network of the European Association of Palliative Care. Br J of Cancer (2001); 84 (5): 587-593.

51. Bruera E. Subcutaneous administration of opioids in the management of cancer pain. In: Foley KM, Bonica JJ, Ventafridda V, eds. Advances in pain research and therapy, vol 16. New York: Raven Press, 1990: 203-18.

52. Urch CE, Field GB, Chamberlain JH. A Comparative study of syringe driver use in community, hospice and hospital. Palliat Med 1996; 10: 75.

53. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manage 1997;13(5):254-61.

54. Portenoy RK, Southam MA, Gupta SK, Lapin J, Layman M, Inturrisi CE, et al. Transdermal fentanyl for cancer pain. Repeated dose pharmacokinetics. Anaesthesiology 1993; 78: 36-43.

55. Donner B, Zenz M, Strumpf M, Raber M. Long-term treatment of cancer pain with transdermal fentanyl. J Pain Sympt Manag 1998; 15: 168-75.

56. De Conno F, Groff L, Brunelli C, Zecca E, Ventafridda V, Ripamonti C. Clinical experience with oral methadone administration in the treatment of pain in 196 advanced cancer patients. J Clin Oncol 1996; 14: 2836-42.

57. Ripamonti C, Bianchi M. The use of methadone for cancer pain. Hematol Oncol Clin North Am June 2002. Volume 16, No. 3.

58. Hanks GW. The clinical usefulness of agonist-antagonistic opioid analgesics in chronic pain. Drug Alcohol Depend. 1987 Dec;20(4):339-46.

59. Lipman AG. Clinically relevant differences among the opioid analgesics Am J Hosp Pharm. 1990 Aug; 47(8 Suppl): S7-13.

60. Kaiko RF, Foley KM, Grabinski PY, Heidrich G, Rogers AG, Inturrisi CE, Reidenberg MM. Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol. 1983 Feb; 13(2): 180-5.

61. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects or oral morphine : An evidence-based report. Expert Working Group of the Research Network of the European Association of Palliative Care. J Clin Oncol 2001; 19 (9): 2542-54.

62. Sykes NP. A volunteer model for the comparison of laxatives in opioid-related constipation. J Pain Sympt Manag 1996; 11: 363-9.

63. Fallon MT, Hanks GW. Morphine constipation and performance status in advanced cancer patients. Palliat Med 1999; 13: 159-160.

63a. Kripke BJ, Finck AJ, Shah NK, Snow JC. Naloxone antagonism after narcotic-supplemented anesthesia. Anesth Analg 1976 Nov-Dev; 55(6):800-5.

64. Cherny NI, Portenoy RK. The management of cancer pain. CA Cancer J Clin 1994;44(5):262-303.

65. Porter J, Jick H. Addiction rare in patients treated with narcotics. (Letter) N Engl J Med 1980;302(2):123.

66. Foley KM. Pharmacological approaches to cancer pain management. In : Advances in Pain Research and Therapy. Pain (Suppl 2) Fourth World Congress on Pain, IASP, ed H Fields p629-653. New York Raven, 1989.

67. Portenoy RK. Adjuvant analgesic agents. Haematol Oncol Clin North Am 10:103-119, 1996.

68. Wiffen P, Collins S, McQuay H, Carroll D et al. Anticonvulsant drugs for acute and chronic pain. Cochrane Database Syst Rev 2000;(3):CD001133.

69. Loblaw D, Laperriere N. Emergency treatment of malignant extradural spinal cord compression : an evidence-based guideline. J Clin Oncol 1998; 16: 1613-24

70. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. Pain 2000 Jul; 87(1):7-17.

71. Jarvis B, Coukell AJ. Mexiletine. A review of its therapeutic use in painful diabetic neuropathy. Drugs 1998 Oct; 56(4):691-707.

72. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, cross-over, double-dose study. J Pain Sympt Manag 2000; 20(4): 246-52.

73. Kannan TR, Saxena A, Bhatnagar S, Barry A. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. J Pain Sympt Manag 2002; 23 (1): 60-65.

74. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, et al. Efficacy of pamidronate in reducing the skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med 1996; 334: 488-93.

75. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol 1993; 11: 59-95.

76. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, te al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocal 19 Aredia Breast Cancer Study Group. N Engl J Med 1996; 335: 1785-91.

77. Bloomfield DJ. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. J Clin Oncol 1998; 16: 1218-25.

78. Mannix K, Ahmedzai SH, Anderson H, Bennett M, Lloyd-Williams M, Wilcock A. Using bisphosphonates to control the pain of bone metastases: evidence based guidelines for palliative care. Palliative Medicine 2000; 14: 455-461.

79. Roth A, Kolaric K. Analgesic activity of calcitonin in patients with painful osteolytic metastases of breast cancer. Oncology 1986; 43:283-7.

80. Greenberg PAC, Hortobagyi G, Smith TL. Long term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 1996, 14: 2197-2205.

81. Ihde DC. Chemotherapy of lung cancer. N Eng J Med 1992; 327: 1434-41.

82. Burris HA, Moore MJ, Anderson J et al. Improvement in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: A randomized trial. J Clin Oncol 1997, 15: 2401-13.

83. Oxford Textbook of Palliative Medicine, 2nd ed. Ed. Doyle D, Hanks G W, MacDonald N. Oxford University Press, 1999.

84. Borgelt B, Gelber R, Kramer S, Brady L W, Chang CH, Davis LW, Perez CA, Hendrickson FR. The palliation of brain metastases: final results of the first two studies by Radiation Therapy Oncology Group. International J of Rad Oncol, Bio, Phy, 1980; 6 (1): 1-9.

85. Loblaw DA, Laperriere NJ. Emergency Treatment of Malignant Extradural Spinal Cord Compression: An Evidence-Based Guideline. J Clin Oncol, 1998 16: 1613-24.

86. Lewington VJ, McEwan AJ, Ackery DM, et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. Eur J Cancer 1991, 27: 954-8.

87. Robinson RG, Preston DF, Schiefelbein M, Baxter KG. Strontium 89 therapy for the palliation of pain due to osseous metastases. JAMA, 1995; 274 (5): 420-4.

88. Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology 1992; 76: 534-40.

89. Polati, E, Finco G, Gottin L, Bassi C, Perdezoli P, Ischia, S. Prospective randomised double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. Br J Surg 1998; 85: 199-201.

90. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a metaanalysis. Anesth Analg 1995, 80: 290-5.

91. Mercadante S. Celiac plexus block versus analgesics in pancreatic cancer pain. Pain. 1993 Feb;52(2):187-92.

92. Brown DL, Bulley CK, Quiel EL. Neurolytic celiac plexus block for pancreatic cancer pain. *Anesth Analg* 1987; 66(9):869-73.202

93. Van Dongen RT, Crul BJ. Paraplegia following coeliac plexus block. Anaesthesia. 1991 Oct;46(10):862-3.

94. Hay RC: Subarachnoid alcohol block in the control of intractable pain: Report of results in 252 patients. Anesth Analg 41:12-16, 1962.

95. Bruno G: Intrathecal alcohol block – experiences in 41 cases. Paraplegia 12:305-306, 1975.

96. Placarte R, Amescua C, Patt R et al: Superior hypogastric plexus block for pelvic cancer pain. Anesthesiology 73: 236, 1990

97. De Leon-Casasola OA, Kent E, Lema MJ: Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain 54:145-151, 1993.

98. Bonica JJ, Buckley FP, Moricca G et al. Neurolytic blockade and hypophysectomy. In Bonica JJ (ed): Management of Pain, ed 2. Philadelphia, Lea and Febiger, 1990, p 1980.

99. Siegfried J, Broggi G: Percutaneous thermocoagulation of the gasserian ganglion in the treatment of the pain in advanced cancer. Adv Pain Res Ther 2:469, 1979.

100. Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. *Lancet* 1979; 1(8115):527-9.

101. Bullingham RES, McQuay HJ, Moore RA. Extradural and intrathecal narcotics. In: Atkinson RS, Hewer CL, editors. Vol. 14. *Recent advances in anesthesia and analgesia.* New York: Churchill Livingstone; 1982. p. 141-56.

102. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. Reg Anesth. 1996 Nov-Dec;21(6):542-56.

103. Plummer JL, Cherry DA, Cousins MJ, Gourlay GK, Onley MM, Evans KH. Long-term spinal administration of morphine in cancer and non-cancer pain: a retrospective study. Pain 1991; 44: 215-20.

104. Vainio A, Tigerstedt I. Opioid treatment for radiating cancer pain: oral administration vs. epidural techniques. Acta Anaesthesiol Scand 1988; 32: 179-85.

105. Sjoberg M, Nitescu P, Appelgren L, Curelaru I. Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain.

Results from a morphine:bupivacaine dose regimen of 0.5:4.75 mg/ml. Anesthesiology. 1994 Feb;80(2):284-97.

106. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D. Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. Pain 1995 Jun;61(3):391-9.

107. Sanders M, Zuurmond W. Safety of unilateral and bilateral percutaneous cervical cordotomy in 80 terminally ill cancer patients. J Clin Oncol 1995; 13: 1509-12

108. Lee MHM, Itoh M, Yang GW, Eason AL. Physical therapy and rehabilitation medicine. In: Bonica JJ, editor. *The management of pain.* 2nd ed. Vol. 2. Philadelphia: Lea & Febiger; 1990. p. 1769-88.

109. Mayer DK. Non-pharmacologic management of pain in the person with cancer. J Adv Nurs 1985; 10(4):325-30.

110. McCaffery M, Beebe A. Pain: clinical manual for nursing practice. St. Louis: CV Mosby Co.; 1989.

111. Vasudevan S, Hegmann K, Moore A, Cerletty S. Physical methods of pain management. In: Raj PP, editor. *Practical management of pain.* 2nd ed. Baltimore: Mosby Year Book Medical Publishers; 1992. p. 669-79.

112. Sjölund BH, Eriksson MBE. Endorphins and analgesia produced by peripheral conditioning stimulation. In: Bonica JJ, Liebeskind DG, Albe-Fessard D, editors. *Proceedings of the Second World Congress on Pain, Montreal, Quebec.* Vol. 3. Advances in pain research and therapy. New York: Raven Press, Ltd.; 1979. p. 587-92.

113. Barbour LA, McGuire DB, Kirchhoff KT. Nonanalgesic methods of pain control used by cancer outpatients. *Oncol Nurs Forum* 1986; 13(6):56-60.

114. Kohl HW, LaPorte RE, Blair SN. Physical activity and cancer. An epidemiological perspective. *Sports Med* 1988; 6:222-37.

115. Avellanosa AM, West CR. Experience with transcutaneous electrical nerve stimulation for relief of intractable pain in cancer patients. *J Med* 1982; 13(3):203-13.

116. Bauer W. Electrical treatment of severe head and neck cancer pain. *Arch Otolaryngol* 1983; 109(6):382-3.

117. McGrath PA, editor. Pain in children: nature, assessment, and treatment. New York: The Guilford Press; 1990.

118. Miser Aw, Dothage JA, Wesley RA, Miser JS. The prevalence of pain in a pediatric and young adult cancer population. Pain 1987; 29(1):73-83.

119. Elliot SC, Miser AW, Dose AM, Betcher DL, O'Fallon JR, Ducos RS, Shah NR, Goh TS, Monzon CM, Tschetter L. Epidemiologic features of pain in pediatric cancer patients: a co-operative community-based study. North Central Cancer Treatment Group and Mayo Clinic. Clin J Pain. 1991; &(4):263-8.

120. Ljungman G, Kreuger A, Gordh T, Berg T, Sorensen S, Rawal N. Treatment of pain in pediatric oncology: a Swedish nationwide survey. Pain 1996; 68(2-3):385-94.

121. WHO guidelines. Cancer pain relief and palliative care in children. World Health Organization, Geneva, 1998.

122. Dahlquist LM, Bushby SM, Slifer KJ, Tucker CL, Eischen S, Hilley L, Sulc W. Distraction for children of different ages who undergo repeated needle sticks. J Pediatr Oncol Nurs 2002:19(1): 22-34.

123. Christensen J, Fatchett D. Promoting parental use of distraction and relaxation in pediatric oncology patients during invasive procedures. J Pediatr Oncol Nurs 2002; 19(4): 127-32.

124. Hester NK., The preoperational child's reaction to immunization. Nursing Res, 1979. 28: p. 250-255.

125. Manne SL, Jacobsen PB, Redd WH. Assessment of acute pediatric pain: do child self-report. Parent ratings and nurse ratings measure the same phenonmenon? Pain 1992; 48(1):45-52.

126. Poulain P., Pichard-Leandri E., Gauvain-Piquard A., Assessment and treatment of pain in children in palliative care. Eur J Palliative Care, 1994. 1: p. 31-35.

127. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987; 66(2): 136-9.

128. AGS Clinical Practice Committee: Management of cancer pain in older patients. J Am Geriatr Soc 1997; 45:1273.

129. Fine PG. Opioid analgesic drugs in older people. Clin Geriatr Med 2001; 17(3):479-485.

130. Herr K, Mobily P, Richardson G et al: Use of experimental pain to compare psychometric properties and usability of pain scales in the adult and older adult populations [abstract]. Annual Meeting of the American Society for Pain Management in Nursing, Orlando, FL, 1998.

131. Parmalee PA. Pain in cognitively impaired older persons. Clin Geriatr Med 1996; 12:473.

132. Parmalee PA, Katz IR, Lawton MP. Pain complaints and cognitive status among elderly institutional residents. J Am Geriatric Soc 1993; 41: 395.

133. Heit HA. The truth about pain management: the difference between a pain patient and an addicted patient. Eur J Pain 2001; 5 Suppl A: 27-9.

134. Drug Enforcement Administration. A joint statement from 21 health organizations and the drug enforcement administration. Promoting pain relief and preventing abuse of pain medications: a critical balancing act. J Pain Symptom Manage 2002 24(2): 147.

135. Breibart W, Dibiase L. Current perspectives on pain in AIDS. Oncology (Huntingt) 2002; 16(7): 964-8

136. Anand A, Carmosino L, Glatt AE. Evaluation of recalcitrant pain in HIV-infected hospitalized patients. J Acquir Immune Defic Syndr. 1994 Jan; 7(1): 52-6.

137. Kimball LR, McCormick WC. The pharmacologic management of pain and discomfort in persons with AIDS near the end of life: use of opioid analgesia in the hospice setting. J Pain Symptom Manage. 1996 Feb;11(2):88-94.

138. Glare PA. Pain in patients with HIV infection: issues for the new millennium. Eur J Pain. 2001;5 Suppl A:43-8

139. Levin ML, Berry JI, Leiter J. Management of pain in terminally ill patients: physician reports of knowledge, attitudes and behaviour. J Pain Symptom Manage 1998:15:27-40.

140. Elliot TE, Murray DM, Oken MM, Johnson KM, Braun BL, Elliot BA et al. Improving cancer pain management in communities: main results form a randomised controlled trial. J Pain Symptom Manage 1997; 13:191-203.

141. Clarke EB, French B, Bilodeau ML, Capasso VC, Edwards A, Empoliti J. Pain management knowledge, attitudes and clinical practice: the impact of nurse' characteristics and education. J Pain Symptom Manage 1996; 11:18-26.

142. Yates PM, Edwards He, Nash RE, Walsh AM, Feniman BJ, Skerman HM, Najiman JM. Barriers to effective cancer pain management: a survey of hospitalised cancer patients in Australia. J Pain Symptom Manage. 2002; 23(5): 393-405.

143. Allard P, Maunsell E, Labbè Johanne, Michel D. Edcational interventions to improve cancer pain control: a systematic review. J Palliat Med 2001; 4(2): 191-203.

144. American Pain Society. Committee of Quality Assurance Standards for pain relief of acute pain and cancer pain. In: Bond MR, Charlton JE, Woolf CJ, editors. Proceedings of the sixth World Congress on Pain. New York: Elservier Science Publications; 1991. p 185-90.

145. Holzheimer A, McMillan Sc, Weitzner M. Improving pain outcomes of hospice patients. Oncol Nurs Form 1999; 26(9):1499-504.

146. Treadwell MJ, Frank LS, Vichinsky E. Using quality improvement strategies to enhance pediatric pain assesment. Int J Qual Health Care 2002; 14(1):39-47.

Annex A List of Resources and Pain Services

A. Resources

1. THE PAIN ASSOCIATION OF SINGAPORE
c/o Dept of Palliative Medicine
National Cancer Centre
11 Hospital Drive
Singapore 169610
Tel: (65) 6436 8183
Fax: (65) 62207490
Website: www.pain.org.sg

2. CANCER EDUCATION AND INFORMATION SERVICE
CANCER HELPLINE
National Cancer Centre
11 Hospital Drive
Singapore 169610
Tel: (65) 62255655
Fax: (65) 63245664
Email: cancerhelpline@nccs.com.sg

B. Institutions with Pain and/or Palliative Care Services

1. ALEXANDRA HOSPITAL
378 Alexandra Road
Singapore 159964
Tel: (65) 64722000
Fax (65) 63793880
Website: www.alexhosp.com.sg

2. CHANGI GENERAL HOSPITAL
2 Simei Street 3
Singapore 529889
Tel: (65) 6788 8833
Fax: (65) 6788 0933
Website: www.cgh.com.sg

3. GLENEAGLES HOSPITAL LTD
6A Napier Road
Singapore 258498
Tel: (65) 6473 7222
Fax: (65) 6475 1832
Website: www.gleneagles.com.sg

4. KK WOMEN'S AND CHILDREN'S HOSPITAL
100 Bukit Timah Road
Singapore 229899
Tel: (65) 6293 4044
Fax: (65) 6293 7933
Website: www.kkh.com.sg

5. MOUNT ELIZABETH HOSPITAL LTD
3 Mount Elizabeth
#02-00
Singapore 228510
Tel: (65) 6737 2666
Fax: (65) 6732 9130
Website: www.mountelizabeth.com.sg

6. NATIONAL CANCER CENTRE
11 Hospital Drive
Singapore 169610
Tel: (65) 6436 8183
Fax: (65) 62207490
Website: www.nccs.com.sg

7. NATIONAL UNIVERSITY HOSPITAL
5 Lower Kent Ridge Road
Singapore 119074
Tel: (65) 6779 5555
Fax: (65) 6779 5678
Website: www.nuh.com.sg

8. SINGAPORE GENERAL HOSPITAL
Outram Road
Singapore 169608
Tel: (65) 6222 3322
Fax: (65) 6224 9221
Website: www.sgh.com.sg

9. TAN TOCK SENG HOSPITAL
11 Jalan Tan Tock Seng
Singapore 308433
Tel: (65) 6256 6011
Fax: (65) 6252 7282
Website: www.ttsh.com.sg

C. Community Hospice Services

1. SINGAPORE HOSPICE COUNCIL
   c/o Assisi Home and Hospice
   820 Thomson Road
   Singapore 574623
   Tel: (65) 6356 6426
   Fax: (65) 6253 5312
   Website: www.singaporehospice.org.sg

2. ASSISI HOME & HOSPICE
   820 Thomson Road
   Singapore 574623
   Tel: (65) 63476446
   Fax: (65) 6253 5312
   Website: www.assisihospice.org

3. BRIGHT VISION HOSPITAL
   5 Lorong Napiri
   Singapore 547530
   Tel: (65) 6248 5755
   Fax: (65) 6881 3872
   Website: www.bvh.org.sg

4. DOVER PARK HOSPICE
   10 Jalan Tan Tock Seng
   Singapore 308436
   Tel: (65) 6355 8200
   Fax: (65) 6258 9007
   Website: www.doverpark.org.sg

5. HOSPICE CARE ASSOCIATION
   12 Jalan Tan Tock Seng
   Singapore 308437
   Tel: (65) 6251 2561
   Fax: (65) 6352 2030
   Website: www.hca.org.sg

6. METHODIST HOSPICE FELLOWSHIP
   No. 70 Barker Road
   #05-01
   Singapore 309936
   Tel: (65) 6478 4700
   Fax: (65) 6478 4701
   Website: www.mws.org.sg

7. METTA WELFARE ASSOCIATION
Block 296 Tampines Street 22
#01-526
Singapore 520296
Tel: (65) 6789 5951
Fax: (65) 6787 7542
Website: www.metta.org.sg

8. SINGAPORE CANCER SOCIETY
15 Enggor Street
#04-01 to 04 Realty Centre
Singapore 079716
Tel: (65) 6221 9577
Fax: (65) 6221 9575
Website: www.cancer.org.sg

9. ST JOSEPH'S HOME & HOSPICE
921 Jurong Road
Singapore 649694
Tel: (65) 6268 0482
Fax: (65) 6268 4787
Website: www.stjh.org.sg

Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process, is not compulsory, and is not intended to "judge" your knowledge. The answers can be found at the end of the questionnaire.

Instruction: Choose the best answer

1. The most accurate judge of the intensity of the patient's pain is
   a. the treating physician
   b. the patient's primary nurse
   c. the patient
   d. the phamacist
   e. the patient's spouse or family

2. The most likely explanation for why a patient with pain would request increased doses of pain medication is
   a. the patient is experiencing increased pain
   b. the patient is experiencing increased anxiety or depression
   c. the patient is requesting more staff attention
   d. the patient's request are related to addiction

3. Analgesia for chronic cancer pain should be given
   a. around the clock on a fixed schedule
   b. only when the patient asks for the medication
   c. only when the nurse or doctor determines that the patient has moderate or greater discomfort

4. The recommended route of administration of opioid analgesics to patients with prolonged cancer related pain is
   a. intravenous
   b. intramuscular
   c. subcutaneous
   d. oral
   e. rectal
   f. epidural

5. Which of the following IV doses of morphine administered over a 4 hour period would be equivalent to 30 mg of oral morphine given every 4 hours?
   a. Morphine 5 mg IV
   b. Morphine 10 mg IV
   c. Morphine 30 mg IV
   d. Morphine 60 mg IV

6. Narcotic/opioid addiction is defined as psychological dependence accompanied by overwhelming concern with obtaining and using narcotics for psychic effect, not for medical reasons. It may occur with or without the physiological changes of tolerance to analgesia and physical dependence (withdrawal). Using this information, how likely is it that opioid addiction will occur as a result if treating pain with opioid analgesics? Circle the number closest to what you consider the correct answer.

   a. <1% b. 5% c. 25% d. 50% e. 75% f. 100%

7. Which of the following analgesic medications is considered the drug of choice for the treatment of prolonged moderate to severe pain for cancer patients?
   a. Hoyle's Cocktail
   b. codeine
   c. morphine
   d. pethidine
   e. methadone
   f. transdermal fentanyl

8. At what stage would you recommend maximum, tolerated narcotic (opioid) analgesic therapy for treatment of severe cancer pain?
   a. prognosis of less than 6 to 12 months
   b. prognosis of less than 3 to 6 months
   c. prognosis of less than 1 month
   d. prognosis of less than 1 week
   e. anytime, regardless of prognosis

Answers:

1. c
2. a
3. a
4. d
5. b
6. a
7. c
8. e

Workgroup Members

These guidelines were developed by a multidisciplinary workgroup brought together by the Council of the Pain Association of Singapore, the local chapter of the International Association for the Study of Pain (IASP).

The members of the workgroup are:

Chairpersons:

Dr Cynthia Goh
Head
Dept of Palliative Medicine
National Cancer Centre

Dr Ho King Hee
Consultant Neurologist and Physician
K H Ho Neurology & Medical Clinic
Gleneagles Medical Centre

Members:

Dr Noreen Chan
Associate Consultant
Dept of Palliative Medicine
National Cancer Centre

Dr Koh Nien Yue
Palliative Care Service
Associate Consultant
Dept of General Medicine
Tan Tock Seng Hospital

Dr Koo Wen Hsin
Deputy Head
Dept of Medical Oncology
National Cancer Centre

Dr Angel Lee Onn Kei
Consultant
Palliative Care Service
Dept of Geriatric Medicine
Tan Tock Seng Hospital

Dr Yoong Chee Seng
Consultant
Dept of Anaesthesia
Changi General Hospital

Advisors:	Ms Lita Chew Pharmacy Manager National Cancer Centre
	Dr Daphne Koh Director of Pain Service Dept of Anaesthesia and Surgical Intensive Care Singapore General Hospital
	Prof Lee Tat Leang Senior Consultant Dept of Anaesthesia National University Hospital
	Dr Pang Weng Sun Head Dept of Geriatric Medicine Alexandra Hospital
	Dr Ting Pui Leong Consultant Anaesthetist & Specialist in Pain Medicine Mount Elizabeth Medical Centre
	Dr Yeo Sow Nam Associate Consultant Dept of Anaesthesia and Surgical Intensive Care Singapore General Hospital
	Dr Yeo Tseng Tsai Unit Head Dept of Neurosurgery National Neuroscience Institute
Secretariat:	Ms Clara Yip Dept of Palliative Medicine National Cancer Centre

MOH CLINICAL PRACTICE GUIDELINES 5/2003

Cancer Pain

Ministry of Health

NMRC National Medical Research Council

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

General

A Patients and their families should be reassured that most cancer pain can be relieved safely and effectively. (pg 12)

Grade A, Level Ib

A Involvement of a multidisciplinary team of specialists is associated with effective analgesia and better health outcomes. (pg 12)

Grade A, Level Ib

GPP Clinicians should assess patients for pain and provide optimal relief throughout the course of illness. (pg 12)

GPP

Evaluation of cancer pain

A Cancer pain should be comprehensively evaluated because this results in improved analgesia. (pg 14)

Grade A, Level Ib

B Health professionals should routinely ask about pain in cancer patients, and the patient's self-report should be the primary source of assessment. (pg 14)

Grade B, Level III

B An accurate assessment should be performed to determine the type and severity of pain and its effect on the patient prior to treatment. (pg 14)

Grade B, Level III

B A simple formal assessment tool should be used in the ongoing assessment of pain. (pg 15)

Grade B, Level III

B Clinicians should be aware of common pain syndromes, because prompt recognition allows early therapy and minimizes the morbidity of unrelieved pain. (pg 15)

Grade B, Level III

B A thorough assessment of the patient's psychosocial state should be carried out. The clinician should look for anxiety and depression and ascertain the patient's beliefs about his or her pain. (pg 15)

Grade B, Level III

B Attention should be given to cultural and ethnic factors which may have a bearing on the patient's response to pain and pain control. (pg 15)

Grade B, Level III

C Sudden severe pain in patients with cancer should be recognized as a medical emergency and patients should be promptly assessed and treated. (pg 13)

Grade C, Level IV

GPP Clinicians should document the efficacy of pain relief at regular intervals after starting or changing treatment. Documentation forms should be readily accessible to all clinicians involved in the patient's care. (pg 14)

GPP

Principles of cancer pain management

B The principles of treatment outlined in the WHO Cancer Pain Relief Programme should be followed when treating pain in patients with cancer. (pg 20)

Grade B, Level III

B Medications for persistent cancer-related pain should be administered on a round-the-clock basis with additional "as needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain. (pg 21)

Grade B, Level III

GPP The simplest dosage schedules and least invasive pain management modalities should be used first. (pg 20)

GPP

GPP Placebos should not be used in the management of cancer pain. (pg 20)

GPP

Choice of analgesic therapy

B A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain. (pg 22)

Grade B, Level III

B If pain severity increases, the next step of the analgesic ladder should be taken. Another analgesic of the same potency should not be used. (pg 23)

Grade B, Level III

A Pharmacologic management of mild pain should include an NSAID or paracetamol at recommended doses, unless there is a contraindication. (pg 22)

Grade A, Level Ia

A Patients receiving an NSAID who are at risk of gastrointestinal side effects should be prescribed famotidine 40 mg twice a day, misoprostol 200µg four times a day, or omeprazole 20 mg once a day. (pg 22)

Grade A, Level Ib

A When pain persists or increases, an opioid should be added to the analgesic regimen. (pg 23)

Grade A, Level Ia

B All patients with moderate to severe pain should receive a trial of an opioid analgesic, regardless of the aetiology of the pain. (pg 23)

Grade B, Level IIa and IIb

B If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, move to step 3 of the analgesic ladder. (pg 23)

Grade B, Level III

Use of Opioids in the treatment of moderate to severe pain

B The opioid of first choice for moderate to severe pain is morphine. (pg 26)

Grade B, Level III

B The optimal route of administration is by mouth. There should ideally be two types of oral formulations: immediate-release for dose titration and controlled-release for maintenance treatment. (pg 26)

Grade B, Level III

B The opioid dose for each patient should be individually titrated to achieve maximum analgesia and minimum side effects. (pg 26)

Grade B, Level III

C Where possible, opioid dose titration should be carried out with an immediate-release morphine preparation given every four hours to maintain constant levels of analgesia (pg 26)

Grade C, Level IV

A Once suitable pain control is achieved by use of immediate-release morphine, conversion to the same total daily dose of controlled-release morphine should be considered. (pg 26)

Grade A, Level Ib

C Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of immediate-release morphine. The breakthrough dose should approximate one-sixth of the total daily dose of oral morphine. (pg 27)

Grade C, Level IV

C If patients are unable to take opioids orally, the rectal, transdermal or subcutaneous route may be used. There is no indication for use of the intramuscular route for chronic cancer pain because the subcutaneous route is associated with less risk and less pain. (pg 27)

Grade C, Level IV

C The average relative potency ratio of oral to parenteral morphine is 1:3. (pg 27)

Grade C, Level IV

B A small proportion of patients develop intolerable side effects with oral morphine. In such patients a change to an alternative opioid or a change in the route of administration should be considered. (pg 27)

Grade B, Level III

A Transdermal fentanyl is an effective alternative to oral morphine, but is best reserved for patients with stable opioid requirements. (pg 28)

Grade A, Level Ib

C Methadone is an effective alternative drug, but is more difficult to use than other opioids because of pronounced inter- and intra-individual differences in its duration of action and relative analgesic potency. Its use by non-specialist practitioners is not recommended. (pg 28)

Grade C, Level IV

B Patients receiving opioid agonists should not be given a mixed agonist-antagonist because of the risk of precipitating a withdrawal syndrome and exacerbation of pain. (pg 28)

Grade B, Level IIb

B Pethidine should not be used if continued opioid use is anticipated. (pg 29)

Grade B, Level IIa

B Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia, or suffer intolerable side-effects, despite the optimal use of systemic opioids and non-opioids. (pg 26)

Grade B, Level III

Specific issues regarding opioid use

A Specific interventions to treat the adverse effects of opioid therapy are efficacious. (pg 30)

Grade A, Level Ib

B Constipation is a common problem associated with long-term opioid administration and should be treated prophylactically. (pg 30)

Grade B, Level III

B When naloxone is given to reverse opioid-induced respiratory depression, it should be titrated to improve respiratory function, but with preservation of analgesia. (pg 31)

Grade B, Level IIb

C Mental clouding or confusion due to opioid toxicity should be managed by reducing the dose of opioid, ensuring adequate hydration and treating the agitation/confusion with a neuroleptic, such as haloperidol. (pg 31)

Grade C, Level IV

B Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence or addiction. (pg 32)

Grade B, Level III

B Patients prescribed opioids for pain should be reassured that they will not become psychologically dependent on or addicted to their opioid analgesia. (pg 32)

Grade B, Level III

Adjuvant drugs

A Patients with neuropathic pain should have a trial of a tricyclic antidepressant and/or an anticonvulsant. (pg 33)

Grade A, Level Ia and Ib

C A trial of steroids should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, and spinal cord compression. (pg 33)

Grade C, Level IV

Bisphosphonates

A Bisphosphonate treatment should be considered in addition to conventional analgesic techniques for all patients with multiple myeloma, and breast cancer patients who have pain due to metastatic bone disease. (pg 34)

Grade A, Level Ia and Ib

Anti-tumour Therapy

C Systemic chemotherapy should be considered for cancers which are highly chemosensitive. (pg 36)

Grade C, Level IV

C Hormonal manipulation may contribute to pain relief in hormone sensitive cancers. (pg 37)

Grade C, Level IV

C Radiotherapy is effective in relieving pain due to tumour infiltration. (pg 37)

Grade C, Level IV

C When using anti-tumour therapy, concomitant use of effective analgesics must not be neglected. (pg 37)

Grade C, Level IV

Interventional Techniques

C Professionals who manage patients with cancer pain should be aware of the range of interventional techniques available for the relief of pain and have access to a specialist pain clinic providing a range of interventional techniques. (pg 39)

Grade C, Level IV

GPP Non-invasive therapies should precede invasive treatments, except in rare instances. (pg 39)

GPP

A Coeliac plexus block should be considered in patients with upper abdominal pain, especially when secondary to pancreatic cancer. (pg 41)

Grade A, Level Ia and Ib

A Epidural, intrathecal and intraventricular opioids should be considered in treatment of cancer pain not controlled with opioids by other routes. (pg 43)

Grade A, Level Ia and Ib

Non-pharmacologic Management: Physical and Psychosocial Modalities

C Cutaneous stimulation techniques, such as application of superficial heat and cold, massage, pressure and vibration, may provide pain relief when the source of pain is associated with muscle tension or spasm. (pg 45)

Grade C, Level IV

A Patients should remain active and participate in self-care when possible. (pg 45)

Grade A, Level Ib

B Prolonged bed-rest for cancer patients should be avoided because prolonged immobilization may lead to joint contractures, muscle atrophy, cardiovascular deconditioning, and other undesirable effects. (pg 45)

Grade B, Level III

A Psychosocial interventions should be used concurrently with pharmacological treatment for pain as part of a multidisciplinary approach to pain management and not as substitutes for analgesics. (pg 46)

Grade A, Level Ib

B Education on effective pain control modalities and correction of misconceptions relating to the use of opioids should be a routine part of patient management. (pg 46)

Grade B, Level III

GPP Pastoral care team members should participate in health care team meetings that discuss the needs and treatment of patients. They should be conversant with community resources that provide spiritual care and support for patients and their families. (pg 44)

GPP

Pain in special populations

B Clinicians should give special attention to the assessment and treatment of pain in special populations, including the very young, the very old, the cognitively impaired, and known or suspected substance abusers. Aggressive pain assessment and management are as necessary for them as for the general population. (pg 47)

Grade B, Level III

B Behavioural observation should be the primary assessment method for preverbal and nonverbal children, and used as an adjunct for assessment of verbal children. (pg 48)

Grade B, Level III

B In older children, assessment includes self-report using age-appropriate scales, such as the faces pain scale, and the numeric rating scale. Observation should be used as an adjunct to self-report. (pg 48)

Grade B, Level IIb

C Oral medication in children with cancer pain should follow the WHO analgesic ladder, with dosage adjustments. The basic principles of opioid use are similar to those in adults. (pg 48)

Grade C, Level IV

GPP Assessment in the cognitively intact elderly patient with cancer pain should be done in ways similar to that of the general adult population. (pg 47)

GPP

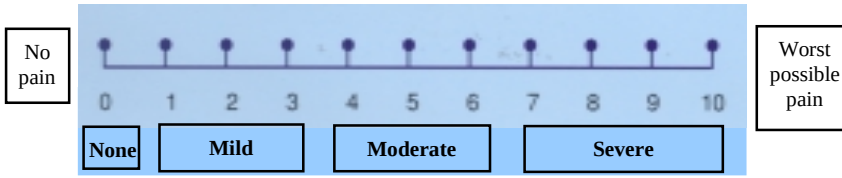
B Behavioural observation should be an adjunct to cancer pain assessment in cognitively impaired adults. (pg 50)

Grade B, Level III

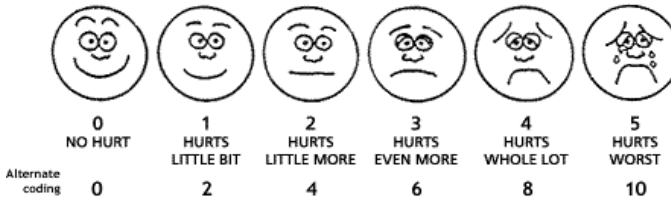
C Non-opioid analgesic modalities should not be substituted for opioid analgesics to treat severe pain in the suspected or known substance abuser. (pg 50)

Grade C, Level IV

Example of a Pain Ruler with the Numeric Rating Scale and Verbal Rating Scale, and the Wong-Baker faces for non-verbal adults and children.



Pain Ruler



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: Wong's Essentials of Pediatric Nursing, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

The WHO Analgesic Ladder for Cancer Pain Management