CLINICAL PRACTICE GUIDELINES

July 2010

MOH/P/PAK/205.10 (GU)

MANAGEMENT OF CANCER PAIN

Ministry of Health Malaysia

Malaysian Association for the Study of Pain

Academy of Medicine of Malaysia

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2010 and will be reviewed in 2014 or sooner if new evidence becomes available.

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Electronic version available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The development group for these Clinical Practice Guidelines (CPG) was from the Ministry of Health (MOH), Ministry of Higher Education and Hospis Malaysia. They consisted of palliative medicine physicians, anaesthesiologists/pain specialists, a clinical oncologist, a general surgeon, a gynae-oncologist, a clinical haematologist, a paediatrician, a paediatric haemato-oncologist, a psychiatrist, a family medicine specialist, a clinical psychologist, a public health physician, a pharmacist, a physiotherapist, a medical social worker and a nursing sister. There was active involvement of the Review Committee during the process of development of these guidelines.

Literature search was carried out at the following electronic databases: PUBMED/MEDLINE, Cochrane Database of Systemic Reviews (CDSR), International Health Technology Assessment websites, Journal full text via OVID search engine, Database of Abstracts of Reviews of Effectiveness and Cochrane Controlled Trials Register (Refer to **Appendix 1** for Search Terms). In addition, the reference lists of all retrieved articles were searched to identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted between 18 September 2008 and 1 March 2010. This date period should be considered the starting point for searching of new evidence for future updates to these guidelines.

Reference was also made to other guidelines on Cancer Pain such as Scottish Intercollegiate Guidelines Network (SIGN) - Control of Pain in Adults with Cancer (November 2008); National Comprehensive Cancer Network (NCCN) CPG in Oncology - Palliative Care (2008), Adult Cancer Pain (2008) and Paediatric Cancer Pain (2007); MOH Singapore CPG - Cancer Pain (2003); and World Health Organization (WHO) - Cancer Pain Relief with a Guide to Opioid Availability (1996). These CPG were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument prior to them being used as references.

The clinical questions were developed under ten major subtopics and members of the development group were assigned individual questions within these subtopics. (Refer to **Appendix 2** for Clinical Questions) The group members met a total of 24 times throughout the development of these guidelines. All literature retrieved was appraised by at least two members and presented in the form of evidence tables and discussed during development group meetings. Later, all statements and recommendations formulated were agreed upon by both the development group and review committee. Where evidence

was insufficient, the recommendations were made by consensus of the development group and review committee. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The articles were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation in these guidelines was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guidelines were posted on the MOH Malaysia official website for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council, MOH Malaysia for review and approval.

OBJECTIVES

To provide evidence-based guidelines to optimise pain control with minimal side effects and adverse outcomes, enhance well being and improve quality of life of patients with cancer pain

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion criteria
Adults and children of all ages with pain from any type of cancer

b. Exclusion criteria
Nil

TARGET GROUP/USER

These guidelines are applicable to all healthcare professionals who are involved in the management of patients with cancer pain:-

- Primary Care Physicians
- Palliative Care Teams
- Anaesthesiologists (Pain Specialists)
- Oncologists
- Clinicians from all other disciplines
- Nurses
- Non-governmental Hospice/Palliative Care Services
- Clinical Psychologists
- Pharmacists
- Physiotherapists
- Occupational Therapists
- Medical Social Workers

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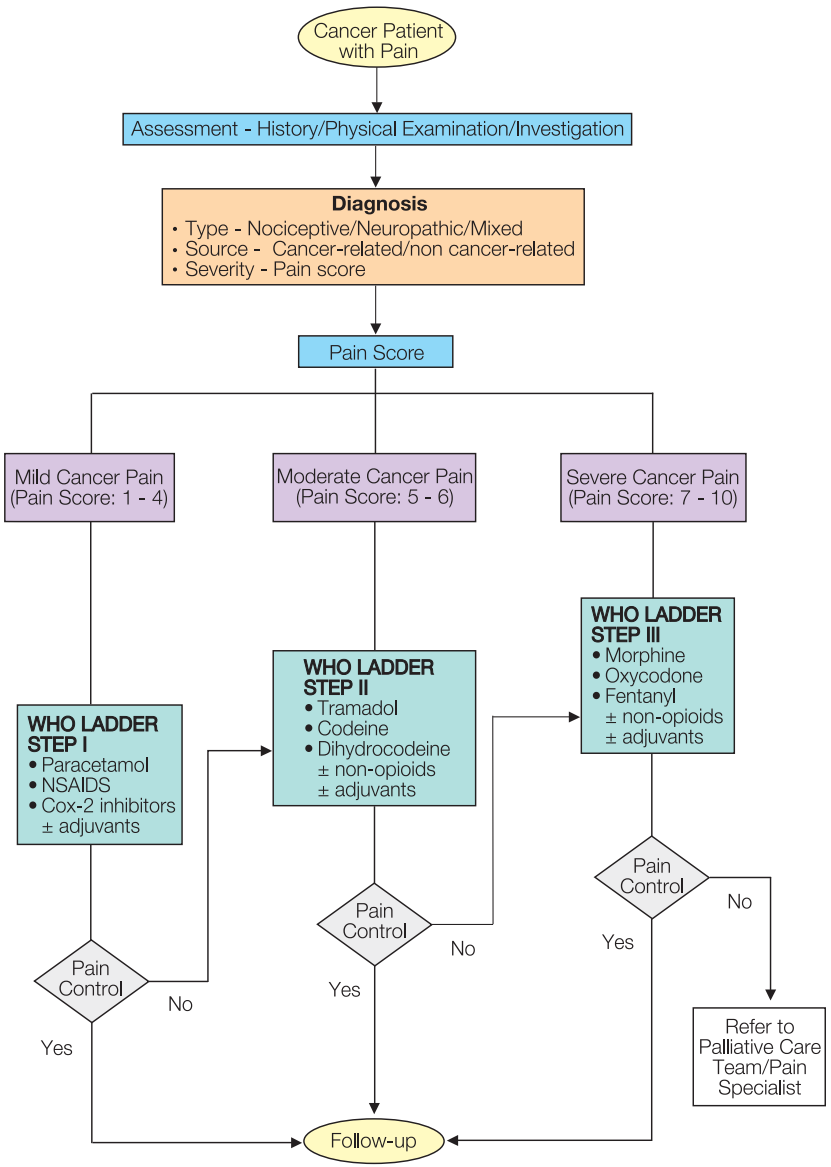
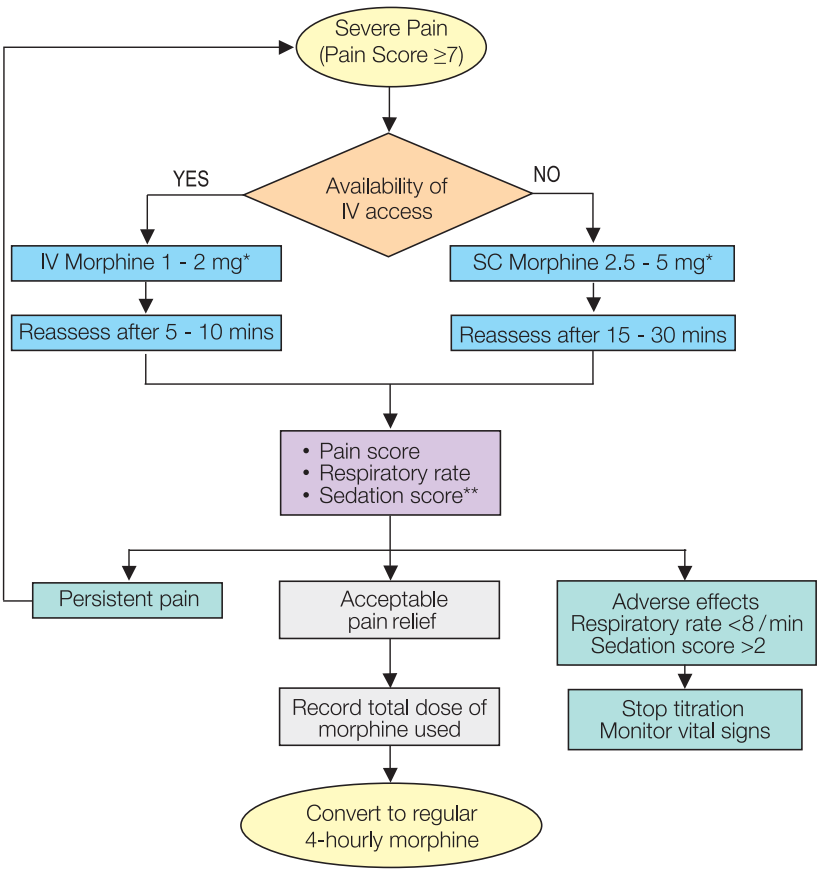
ALGORITHM FOR MANAGEMENT OF CANCER PAIN [2 - 3, level III; 6, level III]



ALGORITHM FOR TITRATION OF MORPHINE FOR RAPID PAIN RELIEF IN ADULTS[1, level III; 4, level I; 5, level III, 7, level I; 8, level II-3]



* For patients already on opioids, the bolus dose of morphine should be 10% of the total 24-hour morphine requirement converted to IV/SC equivalent. For elderly, frail or renal impaired patients, use lower dose of the range given.

** For details on sedation score, see **Appendix 3**.

1. INTRODUCTION

Cancer is a common cause of mortality and morbidity worldwide and in Malaysia; it is the third most common cause of certified deaths in MOH hospitals.[9, level III] In year 2000, it was estimated that some 90,000 Malaysians suffered from cancer.[10, level III] The age-standardised rate (ASR) of cancer incidence for Peninsular Malaysia in 2006 was 128.6 per 100,000 in males and 135.7 per 100,000 in females.[11, level III]

Morbidity due to cancer has been well documented. In a systematic review on symptom prevalence in patients with incurable cancer, pain was the second most common symptom with a pooled prevalence of 71% (95% CI 67 to 74).[12, level III] In a meta-analysis of epidemiological studies of cancer pain, it was shown that the prevalence of pain was 53% (95% CI 43 to 63) in patients with cancer of all stages, 33% (95% CI 21 to 46) in patients after curative treatment and 64% (95% CI 58 to 69) in those with advanced/metastatic cancer.[13, level III] It was also shown that over a third of cancer patients experienced moderate to severe pain (pain score >4/10).

In Malaysia there are no published studies on the prevalence of cancer pain. However, based on global figures, the number of patients with cancer pain in Malaysia is estimated to be about 45,000.[14, level III] In a study done in a Malaysian palliative care unit, 89% of patients with advanced cancer had pain. Of these, 43% reported their pain as moderate to severe (pain score >4), and 57% reported more than one source of pain.[15, level III]

Although pain is a significant source of distress for cancer patients, much of it remains undertreated. In a systematic review on the adequacy of pain management, 43% of cancer patients with pain were undertreated.[16, level III] The World Health Organization states that “Drug treatment is the mainstay of cancer pain management”.[3, level III] Opioid therapy is commonly used and this can be a challenge due to the many barriers amongst patients, the public and healthcare providers which prevent the optimal use of opioid analgesia.[14, level III; 17 - 22, level III] In Malaysia, consumption of morphine in 2007 amounted to 0.94 mg/capita which was considerably lower than the global mean of 5.98 mg/capita.[14, level III; 23, level III] It was estimated that less than 20% of cancer patients in Malaysia who experienced moderate to severe cancer pain received opioid analgesia.[14, level III; 24, level III]

The World Health Organization and the International Association for the Study of Pain have stated that “Pain Relief is a Basic Human Right”.[25, level III]

The MOH Malaysia issued a circular on implementation of pain as the fifth vital sign in 2008 in an effort to make pain more visible as the first step towards improving the management of pain in MOH hospitals.[26, level III]

These Clinical Practice Guidelines aim to work towards these goals by assisting healthcare providers in Malaysia to improve the management of pain in cancer patients.

2. PRINCIPLES OF CANCER PAIN MANAGEMENT

General principles:

- Comprehensive pain assessment prior to treatment
- Understanding the concept of 'total pain'
- Reassessment and adjustment of treatment when indicated
- Inter-professional collaboration in multidisciplinary teams
- Participation of patients and their family members/carers

Comprehensive assessment of pain is the first step to achieve successful cancer pain management for all levels of healthcare providers.[27, 28, level III]

In patients with cancer pain, it is important to understand the concept of 'total pain' as introduced by Dame Cicely Saunders.[29, level III] In 'total pain', patient's pain experience may have physical, psychological, social, emotional, and spiritual components. Effective pain relief can only be achieved if complete and thorough assessments of these components are obtained.

Cancer pain relief is also achieved by understanding the framework of a human person (a unique personal history and inheritance with a complex personal environment) and the use of a four-pronged approach to pain relief including:[30, level III]

i. assessment and reduction of noxious stimulus using measures such as anticancer therapy (chemotherapy, radiotherapy, surgical procedures), adjuvant drugs and nerve-blocking techniques
ii. increasing patient's pain threshold by relieving pathological anxiety, depression, or existential anguish
iii. use of opioid drugs and other analgesics
iv. recognition and treatment of neuropathic pain

The concept of team work and interdisciplinary management of cancer pain is essential in palliative care. Teams consisting of physicians, pharmacists and nurses manage cancer pain better than individual providers.[28, level III] Careful monitoring of pain coupled with adjustment of treatment strategy when indicated and continued assessment of treatment effectiveness are components of effective cancer pain management.[31, level III]

High intensity inter-professional collaboration in managing cancer pain has shown:[32, level III]

- Improvement in mean patient satisfaction (p<0.001)
- Less uncertainty and concerns among patients (p=0.047)
- Adequacy in pain management (p=0.016)

Patients and their families are units of care and issues affecting caregivers can also affect patients' care.[33, level III] Involvement of patients and their family carers in the management of cancer pain reduces barriers to analgesic use ($p<0.0001$) and decreases the worst pain score ($p<0.05$).[34, level I] To further enhance the effectiveness of cancer pain management, adherence to guidelines for cancer pain management has shown to improve pain treatment efficacy as compared to standard care ($p<0.02$).[35, level I]

3. DIAGNOSIS AND ASSESSMENT

Pain is a highly complex and subjective phenomenon. Its components are not only physiological, but also include behavioural, cognitive, emotional, spiritual and social aspects.[27; 36, level III] Effective treatment of pain begins with a comprehensive assessment encompassing these multidimensional components. The interpretation of pain and how the sufferer responds to it behaviourally and emotionally is unique and individualised.

Assessment of pain is a vital step in cancer pain management and is the responsibility of all healthcare providers.[3, level III; 37 - 39, level III] Accurate and comprehensive assessment should be performed prior to treatment in order to plan for appropriate interventions and to assess their effectiveness after initiation.[27; 40]

Pain assessment aims to determine:

i. Nature and pathophysiology of pain
ii. Severity of pain
iii. Impact of pain on functions and quality of life
iv. Response to interventions

Similer to other clinical assessment, a complete pain assessment requires a detailed history, physical examination and relevant investigation.

3.1 CLINICAL PRESENTATION OF CANCER PAIN

Cancer pain can be classified by various schemes according to aetiology, pathophysiology, anatomical location of pain syndrome, temporal pattern and severity.[41, level III] (Refer to **Appendix 4** for Various Schemes for Classifying Cancer Pain) In the clinical context, cancer pain is often described using a combination of these classifications. Clinical characteristics of the pathophysiologic classes of cancer pain are shown in the following **Table 1**.

Table 1. Classification of Cancer Pain Based on Pathophysiology

Nociceptive Pain	➢ Pain that is due to tissue damage associated with an identifiable somatic or visceral lesion.[42, level III] ➢ Subdivided into somatic and visceral types based on nature of tissue injury.[43, level III]
• *Somatic Pain*	- *Damage of somatic tissue such as bones and soft tissue.* - *Character is aching, stabbing or throbbing.* - *Pain is usually well localised.* [41, level III]

• *Visceral pain*	- *Damage is to viscera such as liver, intestines, pancreas, bladder, etc.* - *Character is cramping or gnawing when due to obstruction of hollow viscus.* - *Character is aching, sharp or throbbing when due to tumour involvement of organ capsule.* - *Pain is usually diffuse and difficult to localise.* - *Pain may be referred to somatic structures.* [41, level III]
Neuropathic Pain	➢ Pain is due to abnormal somatosensory processing in the peripheral or central nervous system.[42, level III] ➢ Character is burning, pricking, electric-like, shooting or stabbing, and sometimes may have a deep aching component. ➢ Pain is usually located in the area innervated by the compressed/damaged peripheral nerve, plexus, nerve root or spinal cord. ➢ Pain is often associated with loss of sensation in the painful region. ➢ Allodynia or dysaesthesia may be present.

Knowledge about pain characteristics, syndromes and pathophysiology provide a useful background to understand cancer pain and help to determine appropriate interventions.[43, level III] An international survey of cancer pain characteristics and syndromes by Caraceni A et. al. showed that 92.5% of cancer patients with pain experienced pain due to the cancer itself while 20.8% experienced it due to its treatment. In a small proportion (2.3%) however, pain was not related to cancer or its treatment. This emphasizes the need to assess and differentiate benign causes of pain (such as osteoarthritis, migraine and osteoporosis) which may be managed differently from cancer pain.[43, level III]

That survey also showed that approximately 25% of patients had more than one type of pain and two-thirds (64.8%) experienced episodes of breakthrough pain.[43, level III] In terms of pathophysiology, 71.6% was nociceptive somatic pain, 34.7% nociceptive visceral pain and 39.7% neuropathic pain. A higher pain intensity was significantly associated with presence of breakthrough pain, somatic pain, younger age and lower performance score.

List of Common Pain Syndromes:[42, level III]

- Nociceptive syndromes related to direct tumour involvement
  - Base of skull metastasis
  - Vertebral syndromes

  - Diffuse or multifocal bone pain
  - Pain due to neoplastic involvement of viscera such as liver capsular pain
- Neuropathic syndromes related to direct tumour involvement
  - Peripheral nerve syndromes
  - Brachial and lumbosacral plexopathy
  - Leptomeningeal metastasis
  - Epidural spinal cord, nerve root or cauda equina compression
- Syndromes related to therapy
  - Post-operative pain syndromes such as post-thoracotomy pain
  - Post-radiation syndromes
  - Post-chemotherapy syndromes such as peripheral neuropathy

3.2 CLINICAL ASSESSMENT OF PAIN

3.2.1 History

Taking a good pain history is the key to accurate clinical assessment of pain as majority of pain diagnoses can be made based on history alone.

Table 2. Points for history taking

Characteristics of pain	• Site – single/multiple • Quality – sharp/dull/throbbing/colicky, etc. • Intensity – pain score • Timing – persistent/episodic/on movement/spontaneous • Radiation of pain • Aggravating and relieving factors • Associated symptom – numbness / abnormal sensation / hyperalgesia / allodynia, etc.
Cancer history	• Site(s) – primary/metastatic • Treatment(s) – surgery/chemotherapy/radiotherapy
Medication	• Analgesia • Side effects • Concurrent medications including traditional/alternative medications • Treatment response/adherence
Co-morbidities	• Renal/liver disease • Cardiac/respiratory disease • Cognitive impairment • Other pain conditions – acute/chronic • Previous alcohol or drug abuse
Psychosocial	• Emotional/psychological – depression/anxiety/stress, etc. • Effects on ADL/appetite/sleep • Effects on socio-economics functioning • Perception of pain and pain medications

3.2.2 Physical Examination

In the assessment of cancer pain the physical examination serves to confirm the clinical diagnosis made after taking a comprehensive history and provides a comprehensive understanding of the patient's condition and extent of problems.[2, level III; 44, level III] For patients with suspected neuropathic pain, neurological assessment must be included.

3.2.3 Investigations

In patients with selected painful conditions, investigations may be necessary to clarify the diagnosis and/or assist clinical decision making. These may include radiological investigation such as plain X-rays, bone scans, computerised tomography (CT) scans and magnetic resonance imaging (MRI), and blood investigations such as liver and renal function tests. It must be emphasised that investigations should be ordered judiciously and only if the results could potentially influence clinical management.

3.2.4 Pain Assessment Tools

Appropriate assessment and documentation of pain experiences can improve pain control.[45, level III] Pain assessment tools should be used in the ongoing assessment of pain, both for its intensity and effectiveness of management.[27] Pain assessment tools include unidimensional and multidimensional measures. The most commonly used unidimensional assessment tools are Visual Analogue Scale (VAS), Numerical Rating Scale (NRS) and Verbal Rating Scale (VRS),[46, level II-1] all of which are valid and adequately reliable.[47, level II-1] It is vital to identify the appropriate pain assessment tool for each patient because patients' ability to understand and use the tools, and the careful interpretation of the scores by healthcare professionals are central to successful pain management.[45, level III] Pain assessment using unidimensional scale is easily implemented (with minimal training) and sustained in outpatient practice.[48, level II-1] In the implementation of "Pain as the 5th Vital Sign", the MOH Malaysia has recommended the pain assessment tools listed in **Appendix 5.**

Proxy measures of cancer pain (pain ratings made by someone other than the patient) may be useful when patients are not able to provide pain ratings, but they should not be used as replacements for patient ratings when patient self-report measures are available.[47, level II-1]

Multidimensional measures of pain intensity are reliable, but evidence concerning their validity is lacking.[47, level II-1] Brief Pain Inventory (BPI), with internal consistent coefficient of 0.78 - 0.97, is the most frequently used and free of linguistic/cultural bias. Other multidimensional scales

used include EORTC QLQ-C30 Pain Scale, SF-36 Bodily Pain Scale and the Short Form McGill Pain Questionnaire (SF-MPQ). In Malaysia, multidimensional measures are used mainly in research as they are less practical for day to day clinical use.

A systematic review recommended that the ideal pain assessment tool for patients in palliative care should be precise (high validity and reliability), short and flexible for use in different populations and situations.[49, level II-1]

Although self-report of pain is the gold standard, this may not be the case in cognitively impaired adults, especially those with moderate to severe impairment. In a review which evaluated the tools based on behavioural indicators for pain assessment in nonverbal older adults with dementia, Herr K et. al. concluded that there is no standardised tool that can be recommended.[50, level III] However, the MOH "Pain as the 5th Vital Sign" guidelines recommend the use of the Face Legs Activity Cry Consolability (FLACC) scale for cognitively impaired adults.[37 - 39, level III]

Health care providers looking after cognitively impaired adults should search for potential sources of pain and use behavioural indicators to assess pain. Obvious pain behaviours include grimacing and rubbing the painful part but less obvious behaviours like irritability, aggression or changes in activity pattern and appetite may also indicate pain. Surrogate reporting of pain by carers/family members has also been shown to be accurate ($p=0.014$)[51, level III] and in cases where pain is suspected in a demented person, a trial of analgesics may be warranted.[52, level III]

3.2.5 Psychosocial Assessment

The meaning of pain for patients with cancer may be different compared to those with pain due to non-malignant conditions. Physical pain is perhaps one of the most feared consequences for patients with cancer.[53, level III] In general, the experience of chronic pain may mean loss of control, power and authority, dependence on analgesics and repeated treatments as well as socio-economic threats. In addition, some cancer patients may see pain as a sign of disease progression leading to loss of hope for cure or as a punishment for previous wrong doings. Hence pain has profound effects on mood, anxiety and other psychological symptoms.[54 - 55, level III]

- Pain is an important stressor in all kinds of cancers, causing disability and psychological distress.
- Psychological factors in cancer patients can compound the experience of pain.
- Screening for psychological distress should be administered using validated tools.

Studies which examined the relationship between psychological distress and pain showed that they were significantly related. In a systematic review by Laird BJ et. al., there were significant relationships between cancer pain and depression.[56, level II-2] The mean prevalence of patients with both depression and pain was 36.5% (range 22.1 to 49.0) and pain intensity had positive correlation with depression ($r=0.36$ to 0.51, $p<0.01$). They concluded that both pain and depression are highly prevalent in cancer patients and that psychological distress is more prevalent in cancer patients with pain than those without pain.

Pain was positively associated with psychological distress (OR=1.2 to 6.0) and negatively associated with social support/activities (OR=1.67 to 2.30).[57, level II-2] Compared to the general population, cancer survivors reported a higher symptom burden of recurrent pain, OR=2.44 (95% CI 2.16 to 2.74); psychological distress (depressed and anxious mood), OR=1.98 (95% CI 1.76 to 2.22) and insomnia OR=2.09 (95% CI 1.83 to 2.38).[58, level II-2]

Psychological distress often goes unrecognised, therefore routine screening for psychological distress should be part of a comprehensive pain assessment.[27] The use of simple and practical screening tools may assist the clinicians in recognising the distress and subsequently make necessary referrals for appropriate support.[59 - 60, level III] In a study to determine whether the single-item Distress Thermometer (DT) compared favourably with multiple-item measures used for psychological distress such as Hospital Anxiety and Depression Scale (HADS) and Brief Symptom Inventory (BSI-18), it was found that the DT was able to discriminate effectively between classified patients with and without clinically significant distress.[60, level III] A DT cut-off score of ≥4 yielded sensitivity of 0.77 and specificity of 0.68 for HADS, and sensitivity and specificity of 0.70 for BSI-18. (Refer to **Appendix 6** for Distress Thermometer)

3.3 RELIABILITY OF CANCER PAIN ASSESSMENT

The assessment of a patient's pain is the responsibility of the healthcare professional, but the extent of pain is 'owned' or dependent on the patient's history and recount. It has been shown that healthcare professionals tend to underestimate the level of pain experienced by

patients.[27; 61, level III] The patient therefore is the most reliable assessor of his/her pain provided he/she is competent and able to communicate appropriately.[27]

Assessment of cancer pain by patients and nurses differed significantly in most intense pain (p=0.006) and acceptable pain (p=0.05).[61, level III] Nurses tended to underestimate pain when they had poor knowledge of pain medication in general (p=0.046) and morphine in particular (p=0.043). In addition, specialised nurses with advanced education and knowledge assessed patients' pain more accurately than nurses who did not have this additional training (p<0.05).

A study has also shown that discrepancy between patient and physician in judging severity of patient's pain was predictive of inadequate pain management (OR=2.3).[62, level III] The greater the discrepancy, the more likely pain management was inadequate. Patients with less adequate analgesia reported less pain relief (p<0.001) and greater pain-related impairment of function (p=0.02).

Patients and their families reported parallel perceptions of the patients' cancer pain with positive correlation in patient's pain (r=0.67, p=0.0001) and performance status (r=0.57, p=0.0001) although family members consistently reported higher scores.[63, level III] Family members' assessments of pain are significantly related to appropriate knowledge and attitudes on cancer pain (R^2=0.27).

Recommendation

- Accurate and comprehensive assessment should be performed prior to treatment in all patients with cancer pain. **(Grade C)**
- Unidimensional pain assessment tools such as the NRS, VAS and VRS should be used regularly in the day to day assessment of patients with cancer pain. **(Grade B)**
- Psychosocial assessment should be carried out in all patients with cancer pain. **(Grade B)**
- Patient's self-report provides the most reliable assessment of pain. **(Grade C)**

4. PHARMACOLOGICAL TREATMENT

Effective cancer pain management frequently involves the use of pharmacological agents such as opioid, non-opioid and adjuvant analgesics as part of a multimodal approach which encompasses physical, psychological and social aspects. Clinicians should be familiar with the role of different pharmacological treatment and methods of delivery in order to provide optimal relief to patients with cancer pain.

The basic principle of the pharmacological treatment is "by the mouth, by the clock and by the ladder" i.e.:[3, level III]

- The route of administration is oral as far as possible
- Dosing of analgesic should be according to a fixed time schedule
- The choice of analgesic should be guided by the WHO analgesic ladder

4.1 WHO ANALGESIC LADDER

In 1986, WHO launched a three-step analgesic ladder as a systematic approach to cancer pain control[3, level III] (refer to **Figure 1**). The regimen of analgesia is based on severity of pain starting with simple analgesics for mild pain, and progressing to opioid analgesics for moderate and severe pain. In a large multinational study (n=1,897) using the BPI where cancer pain severity was categorised based on correlation with functional interferences, it was concluded that pain scores of 1 - 4 correlated with mild pain, 5 - 6 moderate and 7 - 10 severe.[6, level III] Similar findings were reported by a more recent study.[64, level III]

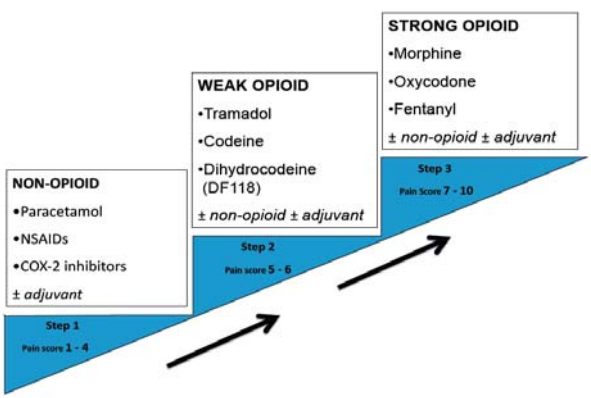


Figure 1. Three-step Analgesic Ladder

Source: Adapted from World Health Organization. Cancer pain relief (Second Edition) with a guide to opioid availability. Geneva: WHO; 1996

In a systematic review of 17 studies on the effectiveness of the WHO analgesic ladder over a period of 20 years after its introduction, successful analgesia ranged from 45 to 100%.[65, level II-2] The WHO analgesic ladder is applicable for long-term pain control in both clinical and home settings.[66, level II-1; 67 - 68, level II-3]

Recommendation

- The treatment of cancer pain in both clinical and home settings should be based on the WHO Analgesic Ladder. **(Grade A)**

Despite its success, the WHO ladder has been challenged especially with regard to Step 2 of the ladder (opioid for mild to moderate pain).[69 - 70, level I; 71, level II-3] Marinangeli F et. al. in 2004 found that the use of strong opioids as first-line treatment in advanced cancer patients with mild to moderate pain had significantly better pain relief (p=0.041), fewer changes in therapy (p=0.001) and greater satisfaction with treatment (p=0.041) than patients treated according to the WHO ladder.[69, level I] Hence, in some cases, omitting step 2 of the WHO ladder and using low-dose strong opioids may be considered appropriate.

4.2 ANALGESICS FOR THE TREATMENT OF CANCER PAIN

4.2.1 Non-opioid analgesics

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended in the first step of the WHO analgesic ladder for mild pain.[3, level III] Paracetamol is generally safe but may cause fatal hepatotoxicity in large doses of more than 10 gram within 24 hours.

NSAIDs are widely used and effective for the treatment of mild to moderate cancer pain.[27] Side effects of NSAIDS are gastrointestinal ulceration, nephrotoxicity and cardiovascular events.[27] The risks increase with long-term use, in the elderly and those with co-morbid medical illnesses. There is no evidence of superiority in terms of efficacy and safety of one NSAID compared to another.[72, level I]

Cox-2 inhibitors, a subclass of NSAIDs, have been shown to be as effective as other NSAIDs for the relief of pain in osteoarthritis and rheumatoid arthritis with significantly improved gastrointestinal safety and tolerability.[73, level I] Although there are no studies done specifically on patients with cancer pain, the same beneficial effect may be extrapolated to such patients. However, the risk of nephrotoxicity and cardiovascular events are the same as with NSAIDS.

In view of potential side effects, it is recommended that the lowest effective dose of NSAIDs or Cox-2 inhibitors should be prescribed for the shortest period to control symptoms.[27] Addition of proton pump

inhibitors or histamine 2 receptor antagonists has been shown to reduce the incidence of NSAID-induced gastro-duodenal ulcers. In elderly patients, NSAIDs and Cox-2 inhibitors should be used with extreme caution.[74, level III]

The use of non-opioid analgesics may result in synergistic effects when used together with opioid analgesics, producing better pain relief and lower incidence of opioid-related side effects. Stockler M et. al. showed that paracetamol improved pain (p=0.03) and well-being (p=0.05) in cancer patients with persistent pain despite concurrent strong opioids, and recommended its addition in all such patients.[75, level I]

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

Recommendation
- Paracetamol or NSAIDs are the drugs of choice for mild cancer pain (Step 1 of the WHO analgesic ladder). **(Grade B)**
- Paracetamol should be used in combination with opioids in the other steps of WHO analgesic ladder unless contraindicated. **(Grade A)**

4.2.2 Weak opioid analgesics

Although the distinction between weak and strong opioids is arbitrary, weak opioids which include tramadol, dihydrocodeine and codeine are mainly used for mild to moderate cancer pain.

The use of tramadol in Step 2 of the WHO Analgesic Ladder is effective.[76, level I] High doses of tramadol (300 - 600 mg per day) are as effective as low dose morphine and cause less constipation, pruritus and neuropsychological symptoms (p<0.05).[77, level I] In clinical practice, the dose of tramadol should not exceed 400 mg per day.[78, level III] Tramadol should be used with caution in patients taking drugs which decrease seizure threshold especially tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenalin reuptake inhibitors (SNRI).[79, level III]

A randomised controlled trial (RCT) using controlled-release (CR) codeine versus placebo showed that codeine resulted in significantly lower overall VAS pain score (22+/-18 mm versus 36+/-20 mm p=0.0001) with reduced rescue analgesia (2.2 +/-2.3 versus 4.6+/- 2.8 tablets per day, p=0.0001).[80, level I] In clinical practice, oral codeine and dihydrocodeine appears to be equipotent.[27]

There is no evidence demonstrating superiority of one weak opioid over another.[27]

Weak opioids are commonly combined with paracetamol for its synergistic effect.[75, level I] Pharmaceutical combination preparations are available and may be used with similar benefits but the dose of opioid is limited by the paracetamol component.

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

Recommendation
- Weak opioids should be used in mild to moderate cancer pain (Step 2 of the WHO analgesic ladder). **(Grade B)**

4.2.3 Strong opioid analgesics

Strong opioids commonly used in Malaysia are morphine, fentanyl and oxycodone. They are recommended for use in moderate to severe cancer pain. Side effects common to all opioids are drowsiness, constipation, nausea, vomiting and pruritus. There is no maximum dose for strong opioids; the appropriate dose is that which relieves pain without major side effects.

There is no evidence to demonstrate superiority of one strong opioid over another in terms of analgesic efficacy.[27]

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

a. Morphine

Oral morphine is first line therapy for moderate to severe cancer pain.[27; 81, level III] It gives good relief of the symptom but with some unwanted effects, mainly constipation, nausea and vomiting.[82, level I] Although effective daily doses have ranged from 25 mg to 2000 mg[82, level I], majority of cancer patients would only require up to 200 mg per day in clinical practice. Morphine is available in immediate-release (IR) and sustained-release (SR) preparations.

The T_{max} of IR and SR oral morphine is 1 hour and 3 hours respectively.[83, level II-3] The T_{max} for IR intravenous (IV) or subcutaneous (SC) is about 10 - 20 minutes.[79, level III] The duration of action of IR and SR morphine is 3 - 6 hours and 12 hours respectively.

Morphine by IV or SC injections are used for rapid onset analgesia (refer to the **Algorithm for Titration of Morphine for Rapid Pain Relief in Adults**) and in patients who are unable to tolerate oral morphine.[4, level I; 7, level I; 81, level III]

b. Fentanyl

Fentanyl is a semi-synthetic opioid with high lipid solubility and available in injection and transdermal patch. Its use in chronic cancer pain management is mainly in the form of a transdermal patch; it should only be considered when patient's opioid requirements are stable.

Transdermal fentanyl is an effective alternative to oral morphine in patients with difficulty in swallowing or having intractable nausea and vomiting whose opioid requirements are stable.[27; 81, level III; 84, level III]

Peak serum levels after application of transdermal fentanyl are achieved within 8 - 12 hours and its half-life is within 16 - 21 hours.[84, level III] It has shown similar efficacy rates when compared with SR oral morphine and oral methadone; number of days to achieve stabilisation in pain score (p=0.65), number of dose changes during titration (p=0.66) and quality of life score (p=0.84).[85, level II-I]

(Refer to **Appendix 8** for Guide for Transdermal Fentanyl Use)

SC or IV fentanyl as a continuous infusion or intermittent bolus can also be used in specific circumstances such as renal failure but preferably under specialist care.[86, level III]

c. Oxycodone

Oxycodone is an alternative strong opioid and available in immediate-release (IR) and controlled-release (CR) oral formulations. Both CR & IR oxycodone are as effective as oral morphine.[81, level III] IR oxycodone has a T_{max} of 1 hour and half-life of 3.5 - 5.7 hours.[87, level III] The CR oxycodone is absorbed in a bi-exponential fashion with a rapid phase half life of 37 minutes and a slow phase half-life of 6.2 hours. This allows onset of analgesia using CR oxycodone within one hour of ingestion and analgesic duration of 12 hours.[27]

Oxycodone demonstrates unequal incomplete cross-tolerance when switching to or from morphine.[87, level III] This is attributable to the combination of kappa opioid receptor binding and mu receptor binding by oxycodone or its metabolite.

Recommendation

- Oral morphine should be the first line therapy for moderate to severe cancer pain. **(Grade C)**
- Oxycodone and fentanyl are alternatives to morphine for moderate to severe cancer pain. **(Grade C)**
- Transdermal fentanyl should only be considered for use when opioid requirements are stable. **(Grade C)**

4.2.4 Opioids requiring special attention

a. Pethidine

Pethidine should not be used for chronic cancer pain management. Its metabolite (norpethidine) may accumulate and cause convulsions with long term use or in high doses.[40; 88, level III] The risk is higher in the elderly and patients with renal impairment. It is believed that long-term pethidine usage may have a higher risk of addiction as it is associated with higher incidence of euphoria.

b. Nalbuphine

Nalbuphine is an opioid agonist-antagonist which should not be used in patients with cancer pain who are already receiving a pure opioid agonist such as morphine, oxycodone or fentanyl. This is because it may reverse the analgesia and may even precipitate a withdrawal reaction when given together with pure opioid agonists.[89, level III]

c. Methadone

Methadone is only occasionally used as an alternative opioid in specialist palliative care settings as its use is more complicated compared to other opioids because of unpredictable plasma half life, analgesic potency and duration of action.[27; 81, level III] Methadone given either by the oral or parenteral route has similar efficacy and adverse effect profile compared to oral or parenteral morphine.[90, level I] Methadone initiation in other settings without specialist advice is not recommended.[27]

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

Recommendation

- Pethidine and nalbuphine should be avoided in chronic cancer pain management. **(Grade C)**

4.3 PRESCRIBING AND TITRATION OF MORPHINE AND OTHER STRONG OPIOIDS

4.3.1 Administration of strong opioids

Morphine is the strong opioid of choice and oral administration is the preferred route.[3, level III; 81 level III] Other strong opioids using various routes of administration may be considered depending on the individual patient's needs and clinical settings.

4.3.2 Initiation, routes of administration and dose titration of morphine

In opioid-naive patients, opioid therapy should start at the lowest level and individualised treatment remains the best method.[71, level II-3] The severity of the pain, the patient's medical condition and the goals of care should determine the rate of dose titration.

The simplest method of dose titration is using regular 4-hourly IR oral morphine and additional similar doses given as needed for breakthrough pain.[81, level III; 91, level II-2] The regular dose is then adjusted to take into account the total daily dose of morphine required within 24 hours.

A dose of 5 mg 4-hourly of IR oral morphine in opioid naive patients and 10 mg 4-hourly in patients tolerant to weak opioids (already on regular tramadol or dihydrocodeine) has been shown to be safe and effective (p<0.01) as a starting dose of morphine therapy.[91, level II-2] In elderly opioid naive patients, a lower starting dose of 2.5 mg 4 - 6-hourly of IR oral morphine (10 - 15 mg in 24 hours) has been shown to be effective (p<0.01) and safe.[71, level II-3]

For patients receiving IR morphine every 4-hours, a double dose at bedtime is recommended for convenience to prevent being woken up by pain at night.[81, level III; 92, level I]

The SC route is useful for patients unable to tolerate oral opioids.[81, level III] There is no difference in efficacy or side effects between continuous infusion and intermittent SC opioids for cancer pain (p>0.05).[86, level I] In patients with severe cancer pain on presentation, titration of opioids can be performed parenterally for rapid onset of analgesia. Intravenous (IV) morphine titration gives faster onset of analgesia compared to traditional oral morphine titration (NNT=2, p<0.001).[7, level I] SC morphine titration has similar efficacy as IV morphine titration (p=0.27)[4, level I] and both methods are safe and tolerated well.[4, level I; 7, level I] For rapid titration of morphine, refer to the **Algorithm for Titration of Morphine for Rapid Pain Relief in Adults.**

Intrathecal and epidural administration of opioids are described in the section on interventional techniques.

Recommendation

- Morphine therapy should be titrated according to individual analgesic response and occurrence of side effects. **(Grade B)**
- Morphine therapy should be initiated at the dose of 5 - 10 mg 4-hourly using the oral IR formulation. **(Grade B)**
- In the elderly, a lower starting dose of 2.5 - 5 mg 4 - 6-hourly of the IR formulation should be used. **(Grade B)**

- Rapid titration using IV or SC morphine is preferred in patients presenting with severe cancer pain for initial control of pain. **(Grade A)**

4.4 MAINTENANCE THERAPY AND BREAKTHROUGH PAIN MANAGEMENT

4.4.1 Maintenance therapy

In patients with chronic cancer pain which is continuous or frequent, regular dosing of opioid therapy or "around the clock" (ATC) dosing should be practiced. Patients on oral IR morphine should receive regular 4-hourly doses to maintain continuous analgesia. Once the effective 24 hours dose is established, the regime may be converted to a 12 hourly SR formulation of the equivalent 24 hour dose.[81, level III] A systematic review on oral morphine for cancer pain found that there were no differences in efficacy between IR and SR morphine.[82, level I]

4.4.2 Breakthrough pain management

- Breakthrough pain is defined as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific trigger (predictable or unpredictable) despite relatively stable and adequately controlled background pain.[93, level II-2; 94, level III]
- Characteristics of breakthrough pain:[27]
  - o rapid onset (reaching maximum severity within 1 to 3 minutes)
  - o short in duration (most subsiding within 30 minutes)
  - o severe in intensity
- Patients on ATC dosing will also require additional 'rescue' medication for breakthrough pain.

The prevalence of breakthrough pain varies between 20 and 90% depending on patient groups and definitions used.[93, level II-2] It has a significant impact on physical, psychological and financial aspects of both patients and carers.[93, level II-2; 95, level III]

It is important to differentiate between breakthrough pain and 'end of dose failure' of regular ATC analgesia.[27] 'End of dose failure' occurs at a similar time each day usually shortly before the next dose of regular analgesia and is caused by an inadequate dose of ATC analgesia. Increasing the ATC dose will address this problem.

There are two subtypes of breakthrough pain i.e. spontaneous and incident pain.[27] Spontaneous pain is sudden and unexpected. On the other hand, incident pain is associated with an activity such as movement and is predictable. Incident pain therefore may be managed

by taking medication prior to the action which precipitates the pain.

Evidence to establish the appropriate dose of morphine for breakthrough pain is lacking. However, the widely accepted ratio of the breakthrough dose to the ATC medication has been 1:6, i.e. equivalent to the 4-hourly opioid doses. In cases where smaller breakthrough doses are required such as in renal impairment, doses as low as 1/12 of the 24-hour dose can be used. This 'rescue' dose may be given as often as required (up to hourly). The ATC dose may be adjusted taking into account the total amount of rescue morphine taken for the last 24 hours.[81, level III]

The evidence on pharmacological treatment of breakthrough pain is limited and involves mainly oral transmucosal fentanyl citrate (OTFC).[96, level I] OTFC however is not available in Malaysia. Although there is no direct evidence investigating the efficacy of morphine for breakthrough pain, two RCTs comparing the effectiveness of OTFC with IR oral morphine and OTFC with IV morphine respectively had demonstrated the efficacy of morphine for breakthrough pain.[97 - 98, level I]

Recommendation

- Patients with chronic cancer pain should receive regular 'around the clock' (ATC) opioid therapy. **(Grade B)**
- Once the effective 24 hours dose is established, patients may be converted to a 12-hourly SR formulation. **(Grade C)**
- Rescue medication for breakthrough pain should be available for all patients with chronic cancer pain at a dose between 1/12 and 1/6 of the total 24-hour dose. **(Grade C)**

4.5 OPIOID SWITCHING (ROTATION)

4.5.1 The practice of opioid switching

Opioid switching refers to changing one opioid with another in order to improve the balance between the analgesic therapy and its side effects. This practice is sometimes necessary particularly when side effects limit further dose escalation of a particular opioid. In one prospective study, it was noted that 34.5% of patients admitted to a palliative care unit required opioid switching.[99, level II-3]

The evidence to support the practice of opioid switching is limited by the lack of proper RCTs and most of the evidences are based on uncontrolled clinical trials and case reports. A systematic review of 31 studies showed that opioid switching in patients with poor response to one opioid improved pain control in more than 50% of patients and improved the balance between analgesia and adverse effects in 70 - 80% of patients.[100, level II-1]

Common indications for opioid switching:[99, level II-3; 101, level III; 102 - 103, level II-1; 104, level III]

- Inadequate pain relief despite appropriate dose titration of the initial opioid
- Intolerable side effects (sedation, nausea, vomiting and constipation)
- Renal impairment
- Practical considerations (patient preference, inability to swallow, etc.)

Opioids which can be used for switching in Malaysia include oxycodone, fentanyl and methadone. Although methadone is the most common opioid used in opioid switching based on available evidence[71, level II-3; 99 - 100, level II-3, 102 - 103, level II-1], a systematic review concluded that no universally safe or effective conversion ratio currently exists for switching to or from methadone.[102, level II-I] It should therefore be used only by palliative care or pain specialists.[81, level III]

When switching to transdermal fentanyl, there is a lag time between application of the patch and onset of analgesia due to the pharmacokinetics of the transdermal preparation.[27] Regular 4-hourly oral opioids should therefore be discontinued 12 hours after application of the patch. Similarly when converting from SR opioid preparations, the patch should be applied together with the last dose of SR medication. A systematic review by Tassinari D et. al. on comparison with SR morphine, transdermal fentanyl showed similar efficacy in pain control, less constipation and laxative consumption (p<0.001), increased patient preference (p=0.014) but significantly higher cost (p=0.0001).[105, level I]

In an opened labeled non-randomised prospective study examining 25 patients who required opioid switching to oxycodone due to inadequate analgesia or intolerable side effects, 84% achieved adequate pain control after switching with significant reduction in pain intensity (p<0.0001) and significant reduction in nausea and drowsiness (p=0.0005 and p=0.03 respectively).[106, level II-3]

4.5.2 Equianalgesic conversion ratio

The issue of establishing optimal equianalgesic dose ratios between different opioids during opioid switching remains unresolved.[102 -103, level II-1; 104, level III]

There are no universally accepted guidelines for equianalgesic conversion and although conversion tables are available they must be used with caution. Frequent reassessment is necessary whenever opioid switching is performed in order to avoid overdosing or under

dosing. A common practice is to reduce the initial converted dose by 25% to 50% due to incomplete cross-tolerance.[27; 101, level III; 107, level III]

Recommendation

- Opioid switching should be considered when side effects limit further dose escalation of a particular opioid. **(Grade B)**
- Conversion from one opioid to another or between different routes of administration should be guided by equianalgesic conversion tables (Table 3). **(Grade B)**

Calculation on dose conversion ratio is shown in **Table 3**.

Table 3. Suggested dose conversion ratio in the direction specified

FROM \ TO	Codeine mg/day	Oral morphine mg/day	SC morphine mg/day	Oxycodone mg/day	Fentanyl TD mcg/h
Oral codeine mg/day		8	20	12	24
Oral morphine mg/day	8		2.5	1.5	3
SC morphine mg/day	20	2.5		0.6	1.2
Oxycodone mg/day	12	1.5	0.6		2
Fentanyl TD mcg/h	24	3	1.2	2	

MULTIPLY DIVIDE

Note: Instructions for using conversion table

1. This conversion chart should only be used as a guide and treatment must be individually tailored for patients based on clinical assessment.
2. Add current opioid dose to get total mg per 24 hours (for fentanyl, note the total hourly rate in mcg)
3. Begin at the left hand column and identify the opioid currently in use
4. Select the alternative opioid from the top row
5. Identify the box where the column and row intersect and determine the conversion factor to divide or multiply in order to obtain 24 hours dose of the alternative opioid
6. Divide 24 hours dose according to dosing frequency required (examples BD dosing divide by 2 and 4-hourly dosing divide by 6)

Example 1:

Conversion of oral morphine to oral oxycodone
Oral morphine mg/day (20 mg 4-hourly = 120 mg per day)
Conversion factor = divide by 1.5
Equivalent dose of oxycodone = 120 ÷ 1.5 = 80 mg per day
Reduce equivalent dose by 25% = 60 mg per day (due to incomplete cross-tolerance)
Therefore dose of SR oxycodone = 30 mg twice daily

Example 2:

Conversion of SC morphine to transdermal fentanyl
SC morphine mg/day (10 mg 4-hourly = 60 mg per day)
Conversion factor = divide by 1.2
Equivalent dose of transdermal fentanyl = 60 ÷ 1.2 = 50 mcg per hour
No dose reduction required (incomplete cross tolerance is already taken into account in the conversion ratio)
Therefore dose of transdermal fentanyl = 50 mcg per hour patch

Additional conversion:
Morphine 40 mg/day PO = Tramadol 200 mg/day PO

Source: Adapted with permission from Sacred Heart Hospice, Sydney New South Wales, Australia

4.6 OPIOID SIDE EFFECTS AND MANAGEMENT

Although opioids are generally well-tolerated and safe, up to 30% of patients on opioids experience troublesome side effects.[108, level III] Awareness and management of these side effects are essential to ensure effective pain management. Management should be directed with the goal of preventing, eliminating or decreasing side effects while ensuring optimal pain control.

Management of opioid side effects includes symptomatic management of individual side effects, opioid switching, and also reduction and adjustment of systemic opioid dosages.[109, level II-1; 110, level III]

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

a. Constipation

Constipation is the most common side effect of opioid therapy.[110, level III] It is recommended that all patients on regular opioid therapy should

receive concurrent prophylaxis for constipation using combination of stimulants and softening laxatives.[27; 109, level II-1] Fentanyl has been shown to cause less constipation compared to morphine and may be a suitable alternative in patients with severe morphine-induced constipation.[84, level II-3; 105, level I]

b. Nausea and vomiting

Nausea and vomiting occur in 15 - 30% of patients on opioids. Tolerance to this side effect commonly develops 5 - 10 days after starting treatment.[27; 108, level III] Commonly used antiemetics include metoclopramide, haloperidol and prochloperazine.[109, level II-1] There are no studies showing superiority of one anti-emetic over another. In refractory cases, a combination of drugs may be used in a multimodal approach with consideration of opioid rotation.[108, level III]

c. Sedation

Sedation most frequently occurs at initiation of opioid therapy but it tends to resolve within a week after that.[108, level III; 109, level II-1] In the majority of patients, symptoms are brief and reassurance plus education is sufficient management. Prolonged sedation may occur with comorbidities such as dementia, metabolic encephalopathy, brain metastases and concomitant use of sedative medication.

Proper opioid titration and using the lowest effective opioid dose reduces the incidence of persistent drowsiness. Management strategies in patients with excessive opioid-induced sedation include dose reduction, changing route of administration, opioid switching and the use of stimulant drugs such as methylphenidate.[40; 110, level III]

d. Confusion and delirium

Mild cognitive impairment may also occur after initiation of opioid therapy but is transient and resolves within 1 - 2 weeks. If persistent or severe, other causes of delirium (e.g. hypercalcaemia, sepsis and other electrolyte imbalance) should be ruled out first. Reducing the dose of opioid by 25% with addition of adjuvant analgesics or opioid switching may resolve the symptoms. Pharmacological treatment with low dose antipsychotics such as haloperidol is also recommended.[109, level II-1; 110, level III]

e. Respiratory depression

Respiratory depression is a **very rare event** in patients with chronic cancer pain when opioids are titrated against pain (a stimulus to respiration).[81, level III] However, the risk is higher when opioids are

rapidly titrated for relief of acute severe pain in cancer patients (Refer to the **Algorithm for Titration of Morphine for Rapid Pain Relief in Adults**).

Monitoring respiratory rate alone may be insufficient to detect respiratory depression from opioid overdose. In a review of opioid-related adverse events in cancer patients, Vila H Jr et. al. found that in 29 patients who required management for opioid overdose, 27 (94%) had decrease in their level of consciousness while only three (10%) had low respiratory rates (<12/min).[111, level II-3] Sedation almost always precedes respiratory depression and therefore the assessment of sedation is a better early clinical indicator of opioid-induced respiratory depression.[112, level II-3]

If severe respiratory depression occurs (respiratory rate <8/minute), very low doses of naloxone (0.04 mg/40 mcg) titrated every 1 - 3 minutes against the patient's respiratory rate can be used. **Large bolus doses of naloxone should not be given** as it reverses the analgesic effect and may precipitate opioid withdrawal.[40; 81, level III]

(Refer to **Appendix 9** for Guide for Naloxone Use)

f. Pruritus and Myoclonus

Pruritus can occasionally occur as a side effect of opioid therapy and antihistamines should be considered as first line treatment. Discontinuing the offending opioid and opioid switching may be necessary if the symptom is severe.[109, level II-1]

Opioid-induced myoclonus is usually a mild clinical problem. Management includes dose reduction, opioid switching and medication to relieve it such as clonazepam, sodium valproate and baclofen.[108, level III; 109, level II-1]

Recommendation

- Opioid-induced side effects should be anticipated and treated adequately to ensure continuous effective opioid therapy. **(Grade B)**
- Patients on regular opioid therapy should receive concurrent prophylaxis for constipation using combination of stimulants and softening laxatives. **(Grade B)**

4.7 RENAL AND LIVER IMPAIRMENT

Renal impairment is commonly encountered in patients with advanced cancer due to age, concomitant illnesses, drug therapy or the cancer itself. Liver impairment may also be seen in patients with malignancy involving the hepatobiliary system or in those with pre-existing liver disease. It is important to recognise the impact of renal and liver

dysfunctions on cancer pain management as the pharmacokinetics of opioid analgesics are altered in these circumstances.

Morphine is metabolised by the liver to morphine-6-glucuronide (M6G) and morphine-3-glucuronide which are excreted by the kidneys. M6G is an active metabolite which accumulates in renal impairment and is associated with respiratory depression and CNS side effects of morphine. In liver impairment, the sedating effects of morphine may be enhanced and may precipitate hepatic encephalopathy. In patients with renal and/or liver impairment, morphine should be used in lower doses and at longer dosing intervals while SR preparations should be avoided.[27; 79, level III; 113 - 114, level III]

The half life of oxycodone is increased and excretion of its metabolites is impaired in renal failure. However there is little data on the adverse clinical effects in these circumstances. In liver impairment, oxycodone may not be converted to inactive metabolites and these results in prolonged action. It should therefore be used with caution and with careful monitoring in patients with renal and liver impairment, and the SR preparation of the drug should be avoided.[27; 79, level III; 113 - 114, level III]

Fentanyl is relatively safe in renal failure as it is metabolised by the liver to inactive metabolites. In liver disease, the metabolism of fentanyl is affected mainly by decreased hepatic blood flow rather than severe hepatic dysfunction and is therefore relatively safe to be used.[27; 79, level III; 113 - 114, level III]

Recommendation

- In patients with renal and/or liver impairment, all opioids should be used with caution and at reduced doses and/or frequency. **(Grade C)**

4.8 TOLERANCE TO OPIOIDS

Tolerance is defined as a phenomenon of adaptation of the body over a period of time in which one or more effects of a drug becomes less with repeated use at the same dose.[115, level III]

Although tolerance to opioid analgesia is known to exist, it is rarely observed in the management of chronic cancer pain. Collin E et. al. observed that there was a relationship between progression of tumour and escalation of morphine doses needed to alleviate pain in cancer patients (r=0.4, p<0.05) and inferred that tolerance to opioids was very unlikely to be involved.[116, level II-3]

Fear of opioid tolerance should not lead to delay in initiating or increasing opioid therapy in cancer patients with pain.[117, level III] However, when

opioid doses are very high (oral morphine >600 mg/day, oral oxycodone > 400 mg/day or transdermal fentanyl >200 mcg/hour), patients should be referred to Pain Specialist or Palliative Medicine Specialist.

Clinicians should not delay initiation or escalation of opioid therapy because of fear of opioid tolerance.

4.9 ADJUVANT DRUGS

Adjuvant analgesics refer to drugs that have primary indications other than pain but have analgesic properties in some painful conditions.[118, level III] They are also known as co-analgesics.[3, level III]

Majority of the trials investigating the role of adjuvant analgesics for neuropathic pain are conducted for chronic non-cancer pain. Although there is some supportive data in cancer pain, the use of anti-neuropathic agents in cancer pain is largely extrapolated from non-cancer pain evidence.

Adjuvant analgesics may be used alone or in combination with other analgesics including strong opioids as shown in **Table 4** below.

Table 4. Adjuvant Drugs Used in Cancer Pain Treatment

Drug class	Examples	Commonly used in the following conditions
Antidepressants	Amitriptyline Duloxetine	Neuropathic pain
Anticonvulsants	Carbamazepine Sodium Valproate Gabapentin Pregabalin	Neuropathic pain
N-Methyl-D-Aspartate (NMDA) Receptor Antagonists	Ketamine	Opioid-poorly responsive pain
Bisphosphonates	Pamidronate Zoledronate Clodronate	Pain from bone metastases
Corticosteroids	Dexamethasone Prednisolone	Pain due to pressure effects related to tumour e.g. brain and liver metastases, spinal cord compression
Anticholinergic	Hyoscine butylbromide	Pain in bowel obstruction

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

4.9.1 Antidepressants

Antidepressants are effective in the treatment of neuropathic pain. The best evidence was for Tricyclic Antidepressants (TCAs). In a systematic review of 31 RCTs, TCAs were effective in reducing neuropathic pain with NNT=4 (95% CI 3 to 5).[119, level I] There was no significant difference in overall effectiveness amongst all TCAs, RR=1.1 (95% CI 0.9 to 1.3). Amitriptyline had the largest number of RCTs and the largest number of patients investigating the role of TCAs for neuropathic pain with NNT=4 (95% CI 3 to 5).

The role of TCAs in neuropathic pain may be limited due to their adverse effects where 20% of patients in the systematic review withdrew because of intolerable adverse effects.[119, level I] For amitriptyline, the NNH for major adverse effects=28 (95% CI 18 to 69) and NNH for minor adverse effects=6 (95% CI 5 to 11).

There was insufficient evidence to recommend SSRIs for neuropathic pain.[119, level I] However, SNRIs was effective in managing neuropathic pain with NNT for venlafaxine=4 (95% CI 3 to 6) and duloxetine=5 (95% CI 3 to 7).[119 - 120, level I]

4.9.2 Anticonvulsants

Anticonvulsants are effective in the management of neuropathic pain. In two separate systematic reviews involving carbamazepine and gabapentin, the NNT was 2 (95% CI 2 to 3)[121, level I] and 5 (95% CI 4 to 6) respectively.[122, level I] In the systematic review on gabapentin, only one study involved the role of gabapentin in cancer-related neuropathic pain where it was found to be effective (p=0.025).[121, level I] The NNH for minor harm for carbamazepine=4 (95% CI 3 to 8) and for gabapentin=4 (95% CI 3 to 6) while NNH for major harm were not statistically significant for both.
There was no significant difference in the overall effectiveness of antidepressants compared to anticonvulsants, RR=1.3 (95% CI 0.9 to 1.8).[119, level I]

Pregabalin was effective in reducing central neuropathic pain associated with spinal cord injury (p<0.001)[123, level I] and for diabetic peripheral neuropathic pain (NNT=5, 95% CI 4 to 8).[120, level I]

4.9.3 Ketamine

Ketamine, an NMDA-receptor antagonist used for general anaesthesia and sedation, can also be used in selected patients whose pain

has been inadequately relieved by opioids alone. However, current evidence from a systematic review is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain.[124, level I]

The available evidence is from two RCTs which showed that ketamine in subanaesthetic doses, used together with morphine, resulted in a significant reduction in pain intensity (p<0.005)[125, level I] and amount of morphine required to control cancer pain (p<0.05)[126, level I] Ketamine may cause psychotomimetic phenomena such as euphoria, dysphasia, nightmares, psychomotor retardation and hallucination as well as delirium.[79, level III]

Patients who respond to ketamine often require dose reduction of their regular opioids by 30 - 50% and close monitoring.[27] Ketamine should therefore be used by specialists familiar with cancer pain management or palliative medicine/pain specialists.

4.9.4 Corticosteroids

Corticosteroids are commonly used for pain related to mass effect of tumour such as headache from brain metastases, abdominal pain from liver capsule distension or intestinal obstruction, and neuropathic pain from spinal cord compression.[127, level III]

There is evidence to support the use of corticosteroids in cancer pain but mostly limited to its use in spinal cord compression. Administration of corticosteroids to terminal cancer patients for eight weeks was shown to have a beneficial effect on pain and quality of life (p<0.05) but with more side effects compared to controls.[128 - 129, level I] In spinal cord compression, there was no significant difference between conventional and high dose dexamethasone on pain reduction.[130, level I]

4.9.5 Hyoscine butylbromide

Bowel obstruction may occur in 2.5 to 51% of patients with advanced cancer.[131, level III] Colicky pain due to inoperable bowel obstruction has been treated empirically with intravenous hyoscine butylbromide, starting dose at around 60 mg/day and titrated upwards.[132, level I]

Recommendations

- Neuropathic cancer pain may be treated with antidepressants and/or anticonvulsants, and the dose should be titrated according to the clinical response and side effects. **(Grade B)**
- Ketamine may be considered in patients with poorly controlled cancer pain despite optimal opioid therapy. **(Grade B)**
- Corticosteroids may be useful in symptom control in patients with advanced cancer. **(Grade C)**

4.10 BISPHOSPHONATES

Bisphosphonates are structural analogues of pyrophosphonates, which are natural components of bone crystal deposition. They are commonly used in hypercalcaemia of malignancy, bone metastasis (with or without hypercalcaemia), and have been found to result in pain relief in some cases. The mechanisms of pain relieving effect of bisphosphonates are poorly understood.

Two meta-analyses found significant pain relief with the use of bisphosphonates (OR= 2.37, 95% CI 1.61 to 3.5 and NNT=6, 95% CI 5 to 11), with best response seen within 12 weeks.[133 - 134, level I] However there is insufficient evidence to recommend bisphosphonates as first line therapy for immediate effect.

Evidence suggests that bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases. No particular drug regimen was found to be superior to another and the effect was not limited to any specific cancer pathology.[133 - 134, level I]

Adverse drug reactions are generally mild, with nausea and vomiting being the most common. NNH for adverse drug reactions requiring discontinuation of therapy was 16 (95% CI 12 to 27).[133, level I] An increased incidence of osteonecrosis of the jaw (ONJ) has been associated with the use of bisphosphonates. Some epidemiological studies had reported the incidence of ONJ to be 0.1 - 1.8% while in others the incidence was much higher at 5 - 10%.[135, level III] Higher doses have also been associated with renal impairment.[136, level I]

- The circumstances under which bisphosphonates should be used still remain unclear. Factors include the severity of pain and whether the disease is widespread or localized. The delayed analgesic effects (benefit at 12 weeks) and serious adverse effects including ONJ and renal impairment should also be considered.
- Monitoring of renal function and calcium levels should be carried out routinely.

Since these agents can be taken for months or years, they can have a significant financial impact. Health economic studies suggest that treating patients with bisphosphonates may result in cost savings by reducing skeletal related events (SREs).[137 - 138, level III] However, due to the high cost of the drugs themselves, the cost-effectiveness ratios for bisphosphonates are not favourable. Furthermore, the cost escalates due to prolonged usage of bisphosphonates as patients live longer with advances in cancer therapy.

(Refer to **Appendix 7** for Suggested Medication Dosages and Side Effects)

Recommendation

- Bisphosphonates may be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases. **(Grade A)**

5. ANTICANCER THERAPY

5.1 RADIOTHERAPY

Radiotherapy is the use of ionising radiation for cancer treatment and it is effective in providing relief from painful bone metastases. It may also exert its effect by inducing tumour shrinkage or growth inhibition. Common dose-fractionation schedules for palliation:

- 6 - 8Gy/ single fraction/ 1 day
- 20Gy/ 5 fractions/ 1 week
- 30Gy/ 10 fractions/ 2 weeks

The role of radiotherapy in controlling cancer pain secondary to bone metastasis has been extensively investigated. Four systematic review (including three meta-analyses) conducted over different time frames had consistently proven its effectiveness.

A systematic review in 1999 estimated 35% partial pain relief (NNT=4) and 25% complete relief (NNT=5) at one month. The estimated time to achieve complete pain relief in 50% patients was more than four weeks and the median duration of pain relief was 12 weeks.[139, level I]

Single fraction radiotherapy was found to be as effective as multiple fraction radiotherapy in controlling cancer pain. Three meta-analyses estimated overall pain relief of 58 - 62% for single fraction and 59% for multi-fraction radiotherapy. Complete pain relief were 23 - 34% for single fraction and 24 - 32% in multiple fractions.[140 - 142, level I]

Two studies showed that single fraction radiotherapy using 4Gy had significant lower overall responses (44 - 59%) compared to 8Gy (69 - 78%).[141, level I]

Higher re-treatment rates had been observed with single fraction compared to multi-fraction radiotherapy; 20% vs 8% (NNH=9)[140, level I] and 21.5% vs 7.4% (NNH=7).[142, level I] The reason is uncertain and may be related to oncologists not willing to re-treat after multi-fraction radiotherapy in view of potential toxicity.

Overall, radiotherapy was well tolerated and there were no observed differences in side effects among the different fractionation groups.[140 - 142, level I]

Hemibody irradiation is radiotherapy given to large segments of the body for patients with widespread bone metastases. A Phase III study showed that 91% of patients achieved at least partial relief of pain, with 45% complete relief.[143, level I] The average time to achieve any pain relief was three days with an average of eight days for maximum relief.

This was well tolerated with 12% grade 3 - 4 toxicity which was mainly haematological in nature.

Apart from painful bone metastasis, radiotherapy is also effective in reducing pain related to advanced malignancies including:[144 - 146, level II-3, 147, level I, 148 - 149, level II-3]

- Thoracic pain from lung cancer
- Abdominal and pelvic pain from gynaecological, gastrointestinal and urological cancers
- Pain due to locally advanced head and neck cancers

The evidence for the above was from retrospective studies on radiotherapy for palliation of symptoms which include pain. The response rates for pain ranged from 67% to 77% and overall symptomatic response rates ranged from 74% to 79%. Palliative hypofractionated radiotherapy schedules were most commonly used. The studies on head and neck cancers emphasised the role of palliative hypofractionated schedules for this group of patients.

The optimal timing of radiotherapy both for painful bone metastasis and pain related to advanced malignancy was not addressed by these studies. However, in view of the effectiveness and high response rates for pain control, radiotherapy should be considered earlier in the course of disease rather than later.

Recommendation

- Radiotherapy is effective and safe, and patients with pain from metastatic bone disease should be referred early to an oncologist. **(Grade A)**
- Single fraction radiotherapy is the preferred schedule for uncomplicated painful bone metastases. **(Grade A)**
- Hemibody irradiation should be considered for patients with widespread bony metastatic disease for rapid pain relief. **(Grade A)**
- Palliative radiotherapy is effective and patients with non-bony pain related to advanced malignancy should be referred to an oncologist early for consideration of radiotherapy. **(Grade B)**

5.2 OTHER ANTICANCER THERAPY

"Best supportive care" without anticancer therapy does not represent the "best" palliative option for advanced cancer.[150, level III]

Systemic chemotherapy and hormonal therapy may be useful strategies to reduce pain and improve quality of life in chemo-sensitive or hormone-sensitive cancers such as breast cancer, prostate cancer, lung cancer, malignant lymphoma, ovarian cancer and germ cell cancer.[150, level III]

Radionuclide therapy such as strontium, samarium and radioactive iodine may be used for metastatic bone pain but its benefits are seen later in comparison to radiotherapy.[151, level III] Due to its high cost and limited availability, this modality is seldom used in this country. The details of the above treatments however are beyond the scope of these guidelines.

6. NON-PHARMACOLOGICAL/NON-INVASIVE TREATMENT

6.1 PSYCHOSOCIAL INTERVENTION

There is emerging evidence that education and cognitive behavioural interventions for cancer pain can alleviate not only pain severity, but also psychological distress related to it.

A meta-analysis on psychoeducational interventions as adjuvant therapy for patients with cancer pain found small to moderate benefits on pain; psychoeducational intervention (d=0.2, NNT=9), cognitive-behavioural intervention (d=0.35, NNT=5) and supportive counseling (d=0.33, NNT=5).[152, level I]

The beneficial effects of the above findings were supported by other studies. Psychoeducational intervention (education on use of analgesia and specific instructions about how to react to uncontrolled pain) increased patients' knowledge regarding cancer pain management (p<0.0001),[153, level I] reduced pain intensity score (p<0.0001) and increased opioid analgesic prescription (p=0.008).[154, level II-1; 155, level I]

In a RCT by Anderson KO et. al., it was shown that brief cognitive behavioural interventions had immediate but non-sustained impact on cancer-related pain.[156, level I] Reduction in pain severity for distraction was 0.90 (95% CI 0.16 to 1.85), and for relaxation was 1.16 (95% CI 0.45 to 1.85).

Specific treatment of anxiety and depression with pharmacological agents may be necessary for successful pain control in patients where these are major issues.

6.2 PHYSICAL AND COMPLEMENTARY THERAPY

Physical and complementary therapies are commonly used to relieve cancer-related symptoms. However the evidence to support their use in the treatment of cancer pain remains limited. Common forms of such therapies available in Malaysia include:-

a. Exercise

Exercise therapy is often used to maintain muscle strength, muscle endurance and reduce joint stiffness. In certain cancer patients, this can help to reduce pain.

One RCT showed that progressive resistance exercise training was effective in decreasing pain (p=0.004), improving muscular strength (p<0.001), muscular endurance (p=0.039), and both active (p=0.001)

and passive (p=0.029) joint range of motion.[157, level I] However, this trial focused only on upper extremity pain and dysfunction in head and neck cancer survivors.

b. Massage and Aromatherapy

Massage with and without aromatherapies were shown to be useful in relieving pain as well as other cancer-related symptoms. However, the benefits were transient.

A systematic review on massage for adult patients with cancer found immediate but short-term (5 - 20 minutes) improvement in pain (effect sizes based on VAS 0.04 - 0.25, NRS 0.13 - 0.66 and BPI 0.33) and other cancer-related distressing symptoms.[158, level I] However, methodological flaws prevented definite conclusion about the efficacy of massage in cancer patients in this systematic review. Another systematic review which included two studies on massage with aromatherapy showed a significant decrease in anxiety levels after massage with aromatherapy compared to massage alone.[159, level I]

c. Acupuncture

Acupuncture was found to be effective in relieving chronic neuropathic cancer pain in a RCT using auricular acupuncture where pain intensity on VAS significantly reduced on day 30 (p=0.02) and day 60 (p<0.001) compared with placebo acupuncture.[160, level I]

d. Transcutaneous Electrical Nerve Stimulation (TENS)

A RCT comparing TENS and transcutaneous spinal electroanalgesia with placebo for chronic pain associated with breast cancer showed no significant difference among the three interventions.[161, level I]

Recommendation

- Psychological interventions, including psychoeducation, are useful and should be considered in patients with cancer pain and psychological distress. **(Grade A)**
- Physical and complementary treatment can be used as an adjunctive therapy for patients with cancer pain. **(Grade A)**

7. INTERVENTIONAL TECHNIQUES

There is a range of interventional techniques available for the relief of cancer pain. These should be considered when conventional therapy fails to provide adequate pain control. Expertise in these techniques is growing and healthcare professionals should be aware of their roles and refer appropriately to trained specialists where available. Patients who should be considered for these interventions include those with significant pain from locally advanced disease, severe neuropathic pain and severe pain on movement.[27]

Interventional techniques used include:

- Neurolytic sympathetic plexus blocks
  - o Coeliac plexus block for pancreatic cancer
  - o Superior hypogastric plexus block for pelvic visceral cancer pain and pancreatic pain
  - o Ganglion impar block for perineal cancer pain
- Intrathecal neurolytic saddle block
- Neuraxial opioid therapy (epidural and intrathecal opioids) ± local anaesthetics for difficult or diffuse pain in advanced cancer
- Vertebroplasty for pain from vertebral secondaries

There are limited numbers of well-designed clinical trials addressing interventional techniques in cancer pain management.

7.1 NEUROLYTIC SYMPATHETIC PLEXUS BLOCKS

These include coeliac, splanchnic and superior hypogastric plexus blocks which involve the instillation of alcohol or phenol with local anesthetics into the nerve plexus. This results in ablation of the sympathetic nerve supply to painful viscera.

A double-blind RCT by Wong et. al. showed that neurolytic coeliac plexus block provided significantly better pain relief in patients with pancreatic cancer compared to optimised systemic analgesic therapy alone (pain levels decreased by 53% vs 27%, $p<0.005$).[162, level I] Another study on the management of abdominal or pelvic cancer pain revealed significant reduction in pain ($p=0.004$), analgesic consumption ($p<0.02$) and adverse opioid-related side effects ($p<0.05$), as well as improved quality of life of patients ($p<0.006$) in those receiving neurolytic coeliac plexus and other sympathetic plexus blocks compared to those having pharmacological therapy only.[163, level II-1]

7.2 NEURAXIAL OPIOID THERAPY

This involves administration of opioid via an intrathecal or epidural catheter with the aid of a syringe pump or an implantable subcutaneous

device. The dose of opioid required to achieve effective analgesia is a fraction of the oral or parenteral dose. When indicated, the opioid may be combined with local anaesthetic and other drugs such as clonidine.

In a cohort study of patients who had received multiple trials of opioids and routes of administration, intrathecal morphine and local anesthetics were shown to provide significant long-term improvement of analgesia (p<0.0001), decreased confusion (p<0.0001) and decreased opioid consumption (p=0.029) until death.[164, level II-2] A Cochrane systematic review of uncontrolled trials on neuraxial opioid therapy showed that epidural, subarachnoid and intracerebroventricular therapy were effective in treating cancer pain that had not been adequately controlled by systemic treatment (excellent pain relief in 62 - 73% of patients).[165, level II-3]

Long term use of epidural and subarachnoid opioids is complicated by catheter-related problems including infection, blockage, dislodgement and misplacement.[165, level II-3] Other adverse effects of systemic opioids can still occur in neuraxial opioid therapy such as nausea, pruritus, urinary retention, constipation, respiratory depression, sedation and confusion.

7.3 VERTEBROPLASTY

This procedure involves the injection of bone cement directly into cancellous bone of the vertebral body in order to relieve pain due to collapse which is caused by osteoporosis or malignant infiltration. It is a percutaneous procedure and relatively safe.

There are no RCTs addressing the role of vertebroplasty in the management of pain from malignant disease of the spine. Current evidence is mainly from multiple case series which indicate an increasing role for percutaneous vertebroplasty in the management of malignant pathological fractures of the spine.[166, level III]

The majority of studies on vertebroplasty were done on osteoporotic vertebral collapse. A systematic review on case series in 2006 showed that the majority of patients had some pain relief after the procedure (87% with vertebroplasty and 92% with kyphoplasty).[167, level II-3]

Cheung G et. al. assessed the effects of vertebroplasty on quality of life in 30 patients with intractable pain from osteoporotic or metastatic fractures and noted significant improvement in patients' pain (p<0.0001), global quality-of-life (p<0.0004) and function (p<0.0008).[168, level II-3]

Two recent well-designed RCTs in patients with painful osteoporotic vertebral fractures showed that improvements in pain and pain-related

disability were similar in both vertebroplasty and sham procedure groups.[169 - 170, level I]

Recommendations

- Neurolytic coeliac plexus block should be considered in patients with pain from pancreatic cancer. **(Grade A)**
- Patients whose pain control is poor despite optimal pharmacological therapy should be referred to specialists trained in interventional pain management. **(Grade B)**
- Patients with uncontrolled bone pain from malignant vertebral collapse should be considered for vertebroplasty where expertise is available. **(Grade C)**

7.4 OTHER SURGICAL INTERVENTIONS

There may be a role for surgical interventions in some chronic cancer pain situations. In bony metastases, depending on the extent of skeletal involvement and the bone involved, orthopaedic interventions such as internal fixation of pathological long bone fractures are warranted to achieve pain relief in patients whose life expectancy is more than four weeks and who are fit for the procedure.[171, level III]

Ablative surgery to remove large tumours such as painful fungating breast lesions or large sarcomas may improve pain control where pharmacological techniques and other interventions provide suboptimal relief. Palliative surgical procedures such as colostomy or bypass procedures may also provide relief from pain as well as other symptoms due to malignant bowel obstruction.

The decision for surgical intervention requires a clear understanding of the goals of care and the condition and prognosis of the individual patient.[172, level III] Decisions should be made by a multidisciplinary team taking into consideration all possible treatment options, risks to the patient and the patient's own wishes.

8. PAEDIATRIC CANCER PAIN

Pain is common in children with cancer and is the presenting symptom in most of them. In one survey, pain was present for a median time of 74 days prior to cancer therapy.[173, level III] Approximately 50% of patients assessed in hospital and 25% of patients assessed in outpatient clinics were found to be experiencing some degree of pain. In another study on patients with advanced disease, the incidence of pain can be as high as 89%.[174, level III]

8.1 ASSESSMENT

With so little research on pain in children with cancer, assessment approaches are borrowed from other pain models e.g. post operative pain. Inherent in borrowing from other pain models are concerns of whether the approaches are appropriate for assessing cancer pain and whether they capture the complexity of the pain experience of these children. Factors influencing the pain experience are:[175, level III]

- the child's disease (pain from disease, invasive procedures, treatment and non-cancer related sources)
- child and family factors (previous pain experience, developmental level, concerns about illness, hospitalisation and death)
- concurrent symptoms (fear, anxiety, loneliness, fatigue and nausea); interplay of these symptoms with pain complicates the pain assessment

The selection of an appropriate clinical pain assessment method should be based on:[176 - 178, level III]

- type of pain or medical condition for which a specific pain assessment tool exists (e.g. post operative or procedural pain)
- developmental age of the child
- validity and reliability of the tool
- specific dimension of pain measured (intensity, location and quality)
- feasibility of use in the clinical setting

Self report methods (e.g. Wong-Baker Faces Scale or Visual Analogue Scale) are considered the gold standard for assessment of pain[39, level III, 177, level III] and can be used as a self report tool by patients and parents.[179, level III]

For younger children and infants who are unable to communicate, well validated infant pain measures such as the FLACC Scale can be used to infer pain.[39, level III; 178, level III] These are multi-item scoring systems comprising either multi-dimensional behavioural indicators or a composite of behavioural, physiological and other indicators of pain.[180, level III] Parent's perspectives should be elicited for infant's usual activities and function, and deviations from normal that may indicate

persistent underlying pain and discomfort.[180, level III] Healthcare providers consistently underestimate children's pain versus self report. Parents also tend to underestimate their children's ratings but their ratings are closer to the children's than nurses.[177, level III; 179, level III]

Distress should be assessed and treated as it reduces coping ability, magnifies psychological trauma and potentiates perception of pain. Psychological interventions such as distraction and imagery can reduce distress and pain.[177, level III]

- Young children with persistent pain may behave with psychomotor inertia.[181, level III]
- Resignation, withdrawal, lack of interest or expression should be recognised as possible pain-related behaviour and treatment with a trial of analgesia should be considered.[181, level III]

(Refer to **Appendix 4** for Pain Scales Recommended for Use in Adults and Paediatrics)

Recommendation
- Accurate pain assessment is essential for appropriate and successful management of cancer pain in children. **(Grade C)**

8.2 TREATMENT

- The principles of cancer pain management in children are similar to that of adults.
- Treatment modalities include analgesic drugs, palliative chemotherapy and radiotherapy and non pharmacological methods.

The WHO analgesic ladder recommends paracetamol and NSAIDS as the first step in the management of cancer pain; however there are no data on the long-term use of these drugs.[182 - 183, level III] NSAIDS are contraindicated in patients with renal impairment or low platelet counts and caution is advised in patients with marrow involvement due to risk of bleeding.[182, level III] Paracetamol is the most frequently used analgesic and the recommended maximum dose is 60 mg/kg/day.[182, level III]

There is no specific study to assess the role of weak opioids such as codeine, tramadol or dextropropoxyphene.[182, level III]

Using morphine in paediatric cancer pain:[182 - 184, level III]
- Oral morphine is the opioid of choice
- Starting doses in opioid naive children:-
  <1 year old : 80 mcg/kg 4-hourly
  1-12 years old : 200 - 400 mcg/kg 4-hourly (not to exceed 5 mg)
  >12 years old : 5 mg 4-hourly

- Dose of breakthrough oral morphine is 50 - 100% of 4-hourly dose and titrated accordingly
- SC and IV routes of administration are alternatives to oral
- Oral to parenteral conversion ratio is 3:1
- Recommended IV morphine infusion rate is 0.02 - 0.03 mg/kg/hr in children over the age of 3 months and 0.015 mg/kg/hr in younger infants

In children of all ages, treatment with morphine is tolerated without severe side effects.[185, level III] Patient-controlled analgesia (PCA) has an established role in paediatric practice, and the safety and efficacy of PCA for mucositis pain after bone marrow transplant has been demonstrated.[182, level III] Parameters such as size of bolus, lockout interval and background infusion rate should be similar to those used for acute pain, except in opioid tolerant patients, where larger doses should be used. Continuous infusion should be considered when oral and intermittent parenteral opioids do not provide satisfactory pain control.[186, level III]

Opioid switching is effective in children who experience dose limiting side effects or who develop tolerance. Drake R et. al. showed 80% of adverse effects resolved after switching.[187, level III]

Transdermal fentanyl is an effective alternative in children already receiving morphine at a stable dose for at least 48 hours[188, level III] and the equianalgesic conversion ratio is similar to adults (refer to **Table 3**). However, it requires close supervision and adequate titration. (Refer to 4.5.1 The practice of opioid switching)

The role of anticonvulsants and steroids has not been appropriately tested in children who experience cancer pain and should be chosen according to general paediatric practice.[182, level III]

Procedural pain can be managed using local anaesthetics, EMLA cream, cooling anaesthetic sprays, sedation and general anaesthesia.[182, level III] IV ketamine-midazolam, administered by trained personnel, is a rapidly reversible and effective modality for painful procedures of any type and number, with minimal morbidity.[189, level II-3]

Recommendation

- Paediatric cancer pain should be managed according to the WHO analgesic ladder. **(Grade B)**
- NSAIDs should be used with caution in children particularly those with bone marrow involvement. **(Grade C)**
- Morphine is the drug of choice for moderate to severe cancer pain in children. **(Grade C)**

9. EDUCATION ON CANCER PAIN MANAGEMENT

9.1 BARRIERS TO EFFECTIVE PAIN MANAGEMENT

Common barriers to effective cancer pain management amongst patients, family/care givers and healthcare professionals include:[14, level III; 17- 22, level III]

- Fear of addiction to opioids
- Fear of drug tolerance
- Fear of adverse effects from analgesics including respiratory depression
- Fatalism about possibility of achieving pain control
- Belief that "good" patients do not complain about pain
- Fear of distracting physician from treating cancer
- Belief that pain signifies disease progression
- Fear of injections
- Difficulty in communicating pain issues
- Inadequate assessment of pain
- Lack of knowledge among healthcare professionals on the use of opioids

Paice JA et. al. showed pain intensity was significantly related to patients' concern about bothering the nurse (p=0.0075) and concern with tolerance and addiction (p<0.005).[190, level III] They also showed that fear of tolerance had significantly greater effects on pain scores compared to fear of addiction (p=0.015). Family members and carers were also most concerned with tolerance (p=0.038).

Among many ethnic groups surveyed, Asian caregivers had significantly more concern regarding tolerance (p=0.025) and about reporting pain (p=0.041).[191, level III] Other factors that contribute to barriers among caregivers are lower education, occupation and employment status. These factors revealed greater fatalism, stoicism beliefs and greater concern about addiction regarding administration of medication (p<0.05).

Barriers also exist among healthcare professionals. Letizia M et. al. found that more than one fourth hospice healthcare providers had concerns about tolerance, fear of the use of morphine, drug side effects and the administration of medications.[191, level III] Sloan PA et. al. highlighted poor knowledge among family physicians on pain assessment, pain relieving factors and eliciting psychosocial background of cancer patients (p<0.0001).[22, level III] In a study to evaluate pain control in three oncology outpatient clinics, Shvartzman et. al. found that physicians overestimated the pain severity but underestimated its impact on everyday life.[192, level III] Patients perceived their pain being undertreated and under-medicated with only 42% reporting adequate pain control.

These findings were due to lack of knowledge and systematic education among the physicians.

In local studies, fears of addiction (36.5%) and respiratory depression (53.1%) as well as poor knowledge on the use of morphine had also been identified among doctors in Malaysian public hospitals.[14, level III; 20, level III]

9.2 EDUCATIONAL STRATEGIES

Education on issues related to cancer pain is an essential element to effective cancer pain management.

Educational strategies should focus on addressing the following issues:
- Understanding cancer pain
- Understanding disease processes and their relation to pain
- How to describe and document pain assessment appropriately
- Understanding pain management
- Awareness of the available analgesics
- Dispelling fears regarding opioid analgesia
- Accessing help and support (when, where and who)

A meta-analysis by Bennett MI et. al. showed that patient-based educational interventions in the form of face-to-face coaching session combined with information booklet resulted in reduced pain intensity (reduction in average pain intensity, WMD= -1.1, 95% CI -1.8 to -0.41; reduction in worst pain intensity, WMD= -0.78, 95% CI -1.21 to -0.35).[193, level I]

Patient-based educational interventions also reduced barriers to analgesic use (p<0.0001), increased adherence to scheduled analgesics use (p<0.0001), reduced the level of pain interference (p=0.0295)[34, level I] and improved patients' willingness to communicate with healthcare professionals regarding pain and reduced patients' concerns about addiction and tolerance in ambulatory settings (p<0.01).[194, level I]

Similarly, continuing education in cancer pain management should also be implemented for healthcare professionals regardless of years in practice.[14, level III; 19 - 20, level III; 22, level III]

Recommendation
- Healthcare professionals have a duty to implement patient-based education interventions to overcome barriers to cancer pain management. **(Grade A)**
- Healthcare professionals involved in cancer care should participate in continuing professional development regardless of years in practice. **(Grade C)**

10. FOLLOW-UP

Follow-up of patients with cancer pain may take place at home, primary care clinics or specialised outpatient clinics including palliative care and cancer pain clinics.

In addition to the various roles and care provided by health care professionals and family caregivers in the follow-up of cancer patients, social workers may assist by assessing and assisting patients to change their attitude if this is a problem. Social workers can also help these patients develop skills such as problem solving, better communication and advocacy which will assist them in either the home or the ambulatory care setting.[195, level III]

10.1 HOME CARE

A home care system with physicians skilled in palliative care using WHO guidelines enables patients to receive pain treatment in the comfort of their own homes and significantly improves pain intensity (p<0.05).[66, level II-3]

Some of the challenges in putting pain management regimes into practice at home include:[196, level III]

- Obtaining prescribed medications
- Accessing information
- Managing side effects
- Coping with and understanding complex information
- Managing new unusual pain
- Managing multiple symptoms simultaneously

In addition, caregivers at home had significantly higher levels of concern in fatalistic beliefs (p=0.008) and addiction (p=0.006) compared to caregivers in skilled care facilities.[191, level III] Caregivers' reservations or misinformation regarding pain management or administration of medication can affect patients' care, more so when it is not addressed.[33, level III] Despite the above issues, a study showed palliative care at home had a positive effect on pain intensity (p<0.0001).[197, level III]

10.2 AMBULATORY CARE

Family physicians play an important role in cancer care, including informing the patient of the diagnosis, helping with treatment decision-making, providing psychological support and treating intercurrent illness.[198, level III] They also recognise and manage complications of cancer and cancer therapies which includes providing appropriate pain management.

In patients living in the community who have no access to hospice home care, the outpatient palliative care clinic is a key link in the chain of continuity of palliative care. Benefits include meeting the palliative needs of the community patients, avoiding unnecessary hospital admissions, providing follow-up and continuity of care, and improving symptom management.[199, level III]

In developing countries with limited resources, the establishment of cancer pain clinics has shown a reduction of overall pain scores by using WHO guidelines and overcoming barriers to effective cancer pain management.[200, level III]

A study had also shown that multidisciplinary clinic assessment on cancer pain resulted in significant improvement in pain (p<0.0001) and well being (p<0.05) of the patients.[201, level III]

(Refer to **Appendix 10** for Pain Management and Palliative Care Service Providers)

Recommendation

- Patients with cancer pain must have regular follow-up either at home, primary care clinics or specialised outpatient clinics including palliative care and cancer pain clinics according to their preferences or circumstances. **(Grade C)**
- Cancer pain management at home can be done by trained healthcare professionals using WHO guidelines and should address concerns of both patients and caregivers. **(Grade C)**
- Social workers should be engaged to help in providing practical assistance and social support to patients with cancer pain. **(Grade C)**

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Appendix 1

SEARCH TERMS

The following MeSH terms or free text terms were used either singly or in combination:

"Neoplasms"[Mesh], tumors, cancers, "Pain"[Mesh], "Prevalence"[Mesh], "Signs & symptoms"[Mesh], "Syndrome"[Mesh], "Diagnosis"[Mesh], presentation, "physical assessment", "Pain Measurement"[Mesh], "pain scale'', reliability, validity, psychological, psychosocial, assessment, "cognitively impaired', "psychological distress", distress, "Emotions"[Mesh] "Nursing"[Mesh], "prime assessor", "Palliative Care"[Mesh], "supportive care'', "cancer pain management", "Patient-Centered Care"[Mesh], "Patient Care"[Mesh], "Family"[Mesh], "Patient Care Team"[Mesh], ""Patient Care Management"[Mesh], "Primary Health Care"[Mesh], "Physicians, Family"[Mesh]), interdisciplinary, Education"[Mesh], outcome, barrier, "Health Services"[Mesh], principle, "Organization and Administration"[Mesh], "World Health Organization"[Mesh], "Guideline "[Publication Type], "cancer pain ladder", "Drug Therapy"[Mesh], "Analgesics, Opioid"[Mesh], "administration and dosage"[Subheading], titration, "breakthrough pain", "Drug Tolerance"[Mesh], "Adjuvants, Pharmaceutic"[Mesh], "adjuvant analgesics", "pregabalin "[Substance Name], "Ketamine"[Mesh], "Dexamethasone"[Mesh], corticosteroid, "opioid rotation", "opioid switching", "alternative opioid", "Diphosphonates"[Mesh], bisphosphonate, "Sedation score", "Morphine protocol", "Radiotherapy"[Mesh], "Soft Tissue Neoplasms"[Mesh], "Behavior Therapy"[Mesh], "Cognitive Therapy"[Mesh], "Physical Therapy Modalities"[Mesh], "Acupuncture"[Mesh], "Massage"[Mesh], "Exercise"[Mesh], "Exercise"[Mesh], "Nerve Block"[Mesh], "Injections, Spinal"[Mesh], "intrathecal therapy", "Vertebroplasty"[Mesh], "follow-up", "Physician's Role "[Mesh], "community care", "home program*", "general practitioner", hospice, "pain clinic", "Outpatients"[Mesh], "Outpatient Clinics, Hospital"[Mesh], "Ambulatory Care"[Mesh],

Appendix 2

CLINICAL QUESTIONS

1. What are the epidemiological characteristics of cancer-related pain including pain caused by cancer and its treatment?

2. What are the clinical presentations of cancer-related pain?

3. What are the methods used for clinical assessment of cancer pain and what is their reliability and validity?

4. How important is accurate assessment of the cancer pain, causes and treatment? What are the domains of comprehensive assessment of cancer pain? How and when to do assessment of cancer pain?

5. Who should be the prime assessor of the cancer pain?

6. What are the barriers/impediments to adequate/effective pain management? What are the optimal strategies to overcome these?

7. What are the principles of management of pain in patients with cancer?

8. Do patients' wishes and goals on management of their cancer pain help to determine effective cancer pain management?

9. What is the WHO Analgesic Ladder? What are its principles? Is it effective to be used in clinical practice?

10. What are the appropriate drugs and their efficacy for different types of cancer pain?

11. What are the side effects and toxicity of these drugs and their management?

12. What are the prescribing, titration and maintenance issues of morphine and other strong opioids?

13. What are the clinical issues related to tolerance to opioids?

14. What are the pharmacological strategies for breakthrough pain and other acute pain crises?

15. What are the adjuvant analgesics in cancer pain management?

16. Are different analgesic drug formulations and routes of administration associated with different patient preferences or efficacy rates?

17. What are the roles of anti-cancer therapy in the management of cancer pain?

18. What are the roles of non-pharmacological/non-invasive therapy in the management of cancer pain?

19. What are the relative efficacy and safety of current invasive treatments for the treatment of cancer-related pain?

20. What are the clinical issues/responsibilities in community cancer pain management?

21. What are the roles of different agencies in cancer pain management?

22. What are the issues related to cancer pain in paediatrics?

Appendix 3

SEDATION SCORE

Score	Sedation level	Clinical findings
0	None	Patient is awake and alert
1	Mild	Occasionally drowsy, easy to rouse, and can stay awake once awoken
2	Moderate	Constantly drowsy, still easy to rouse, unable to stay awake once awoken
3	Severe	Somnolent, difficult to rouse, severe respiratory depression

Source: Macintyre PE & Schug SA. Acute Pain Management: A Practical Guide. Saunders Elsevier: London; 2007

Appendix 4

VARIOUS SCHEMES FOR CLASSIFYING CANCER PAIN

Aetiologic classification	Primarily caused by cancer Treatment of cancer Debility Concurrent pathology (non-cancer related)
Pathophysiologic classification	Nociceptive (somatic, visceral) Neuropathic Mixed pathophysiology Psychogenic
Location of cancer pain syndromes	Head and neck pain Chest wall syndromes Vertebral and radicular pain Abdominal or pelvic pain Extremity pain (such as brachial plexopathy or bony spread)
Temporal classification	Acute Breakthrough Chronic
Severity-based	Mild Moderate Severe

Source: de Leon-Casasola OA. Cancer Pain Pharmacologic, Interventional, and Palliative Approaches. Philadelphia: Saunders Elsevier; 2006

Appendix 5

PAIN SCALES RECOMMENDED FOR USE IN ADULTS AND PAEDIATRICS

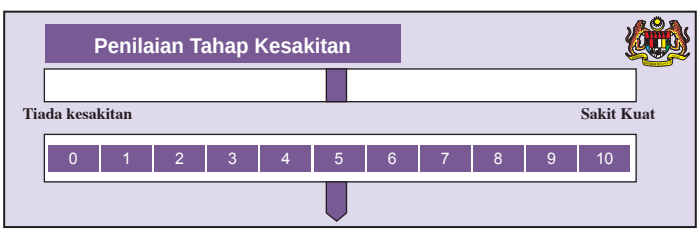
1. For adult patients, use the combined Numerical Rating Scale/Visual Analogue Scale (NRS/VAS)
2. For paediatric patients 1 month to 3 years old, use the FLACC Scale
3. For paediatric patients >3 - 7 old years, use the Wong-Baker Faces Scale
4. For paediatric patients >7 years old, use the combined NRS/VAS Scale (same as for adults)

Note:

i. All scales are scored from 0 (zero) to 10 (ten)
ii. Always use the same scale for the same patient

Descriptions of Pain Scales Used

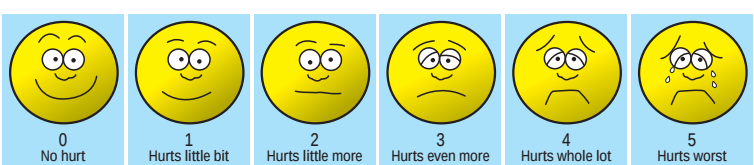
1. Combined Numerical Rating/Visual Analogue Scale



The patient is asked rate his/her pain on a numerical scale where zero (0) is no pain and ten (10) is the worst pain imaginable. In order to assist the patient, he/she can is asked to slide the indicator along the scale to show the severity of his/her pain.

2. Wong-Baker Faces Scale

Patient is asked to choose a face which best describes his/her pain. The number on the face chosen is multiplied by two to give a score from zero to 10.



The Wong-Baker faces scale (adapted from Wong DL et *al, eds, Whaley and Wong's essentials of pediatric nursing.* 5th ed. St Louis, MO: Mosby, 2001)

3. FLACC Scale

Rating scale to be used for children less than 3 years of age or other patients who cannot self-report. Can also be used in cognitively impaired or demented adults.

Category	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to distractable	Difficult to console

Each of the five categories (F) face, (L) legs, (A) activity, (C) cry and (C) consolability is scored from 0 - 2, resulting in total range of 0 - 10

Source:

i. Ministry of Health Malaysia. PAIN as the 5th Vital Sign Guidelines for DOCTORS Management of Adult Patients. Putrajaya: MOH; 2008

ii. Ministry of Health Malaysia. PAIN as the 5th Vital Sign Guidelines for Management of Peadiatrics Patients. Putrajaya: MOH; 2008

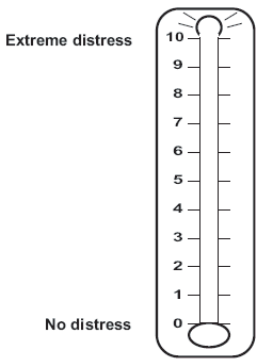
iii. Ministry of Health Malaysia. PAIN as the 5th Vital Sign Guidelines for NURSES Management of Peadiatrics Patients. Putrajaya: MOH; 2008

Appendix 6

DISTRESS THERMOMETER SCREENING TOOL

SCREENING TOOLS FOR MEASURING DISTRESS

Instructions: First please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.



Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

YES	NO	Practical Problems
❑	❑	Child care
❑	❑	Housing
❑	❑	Insurance/financial
❑	❑	Transportation
❑	❑	Work/school
		Family Problems
❑	❑	Dealing with children
❑	❑	Dealing with partner
❑	❑	Ability to have children
		Emotional Problems
❑	❑	Depression
❑	❑	Fears
❑	❑	Nervousness
❑	❑	Sadness
❑	❑	Worry
❑	❑	Loss of interest in usual activities
❑	❑	**Spiritual/religious concerns**

YES	NO	Physical Problems
❑	❑	Appearance
❑	❑	Bathing/dressing
❑	❑	Breathing
❑	❑	Changes in urination
❑	❑	Constipation
❑	❑	Diarrhea
❑	❑	Eating
❑	❑	Fatigue
❑	❑	Feeling Swollen
❑	❑	Fevers
❑	❑	Getting around
❑	❑	Indigestion
❑	❑	Memory/concentration
❑	❑	Mouth sores
❑	❑	Nausea
❑	❑	Nose dry/congested
❑	❑	Pain
❑	❑	Sexual
❑	❑	Skin dry/itchy
❑	❑	Sleep
❑	❑	Tingling in hands/feet

Other Problems: _____

_____

Source:

Reproduced with permission from The NCCN 1.2010 Distress Management Clinical Practice Guidelines in Oncology. ©National Comprehensive Cancer Network, 2010. Available at: http://www.nccn.org. Accessed [January 6, 2010] To view the most recent and complete version of the guideline, go online to www.nccn.org

SUGGESTED MEDICATION DOSAGES AND SIDE EFFECTS

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
Simple analgesic	Paracetamol	0.5 - 1gm, 6 - 8-hourly Max: 4gm/day	Rare	Hepatic impairment, alcohol dependence	Preferred drug particularly in elderly patients. Liver damage following over dosage.
Non-Selective NSAIDs	Ibuprofen	200 - 400 mg, 8-hourly Max: 2400 mg/day	Peptic ulcer GI bleed Platelet dysfunction Renal failure Hypertension Allergic reaction in susceptible individuals Increase in CVS events	Gastroduodenal ulcer Asthma Bleeding disorder Renal dysfunction Ischaemic heart disease Cerebrovascular disease Inflammatory bowel disease	Current data suggest that increased CV risk may be an effect of the NSAID/coxib class. Physicians and patients should weigh the benefits and risks of NSAID/coxib therapy.
	Mefenemic Acid	250 - 500 mg, 8-hourly			
	Diclofenac Sodium	50 - 150 mg daily, 8 - 12-hourly Max: 200 mg/day Drops: 1 drop = 0.5 mg Children ≥ 1 year: 0.5 - 2 mg/kg/day in divided dose Max: 3 mg/kg/day Not indicated for <1 year			
	Diclofenac Potassium	50 - 150 mg daily, 8 - 12-hourly Max: 200 mg/day			
	Meloxicam	7.5 - 15 mg daily Max: 15 mg/day			

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
Selective Cox-2 Inhibitors	Celecoxib	200 - 400 mg, 12 - 24-hourly Max: 800 mg/day	Renal impairment Allergic reaction in susceptible individuals Increase in CVS events	Ischaemic heart disease Cerebrovascular disease Contraindicated in hypersensitivity to sulfonamides	Associated with a lower risk of serious upper gastrointestinal side effects
	Etoricoxib	60 - 90 mg daily 120 mg daily in acute pain Max: 90 /day Long term use should be limited to a maximum of 90 mg daily. 120 mg daily may be used for acute pain relief but for short term only.	Hypertension Renal impairment Increase in CVS events	Uncontrolled hypertension Ischaemic heart disease Cerebrovascular disease	
Weak opioids	Tramadol	50 - 100 mg, 6 - 8-hourly Max: 400 mg/day	Dizziness Nausea Vomiting Constipation Drowsiness	Risk of seizures in patients with history of seizures and with high doses In elderly, start at lowest dose (50 mg) and maximum of 300 mg daily	Interaction with TCA, SSRI and SNRI
	Dihydrocodeine tartrate (DF118)	30 - 60 mg, 6 - 8-hourly Max: 240 mg/day	Nausea Vomiting Constipation Drowsiness	Respiratory depression Acute alcoholism Paralytic ileus Raised intracranial pressure	

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
Combinations of opioids and paracetamol	Paracetamol 500 mg + codeine 8 mg (Panadeine®)	1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day	Constipation	Reduce dose in elderly	Decrease in side effect profile of tramadol and paracetamol while maintaining efficacy
	Paracetamol 325 mg + tramadol 37.5 mg (Ultracet®)	1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day	Nausea Vomiting Drowsiness	Hepatic impairment Renal impairment Alcohol dependence Epilepsy	
Strong opioids	Morphine	Starting dose (oral): 5 - 10 mg, 4-hourly of IR Elderly: 2.5 - 5 mg, 4 - 6-hourly of IR SR oral morphine: to be given in 12-hourly dosing	Common: Nausea Vomiting Drowsiness Constipation Sedation Not common in cancer pain: Sweating Euphoria Respiratory depression Pruritus Myoclonus	Acute bronchial asthma Respiratory depression Dose adjustment for renal impairment and head injuries	Transdermal fentanyl - • Not to be used unless opioid dose is stable. Minimum dose: 12 mcg/hr=30 mg oral morphine in 24 hrs • Not to be used in opioid naive patients
	Transdermal fentanyl	Equianalgesic dose of total 24 hours opioid requirement (refer Conversion Table (Table 3)			
	Oxycodone	Starting dose (oral): 5 mg of IR 4 - 6-hourly CR oxycodone: to be given 12-hourly dosing			
Antidepressant	Amitriptyline	Start with 10 - 25 mg nocte. Increase weekly by 25 mg/day to a max of 150 mg/day	Anticholinergic effects e.g. dry mouth, drowsiness, urinary retention, arrhythmias	Not recommended in elderly patients with cardiac disease, glaucoma, renal disease	Nortriptyline may be a suitable alternative and better tolerated in elderly at similar doses. Interaction with tramadol

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
	Duloxetine	30 - 60 mg/day Max: 120 mg/day	Gastrointestinal disorder Excessive sweating CNS disorder	Narrow-angle glaucoma Potent CYP1A2 inhibitors Concomitant use of MAOIs Hypertension	Interaction with tramadol
Anticonvulsants	Carbamazepine	100 - 1600 mg/day	Dizziness Allergic reaction Ataxia Fatigue Leucopenia Nausea Vomiting Drowsiness	Increased ocular pressure Latent psychosis Confusion Agitation	
	Gabapentin	Day 1: start at 300 mg nocte Day 2: 300 mg 12-hourly Day 3: 300 mg 8-hourly Thereafter, increase by 300 mg/day every 1-7 days Max: 2400 mg/day	Drowsiness, dizziness GI symptoms Mild peripheral oedema	Dose adjustment needed in renal impairment	Well tolerated. Serious adverse events are rare.
	Pregabalin	Start with 150 mg/day (in 2 divided doses). If needed, increase to 300 mg/day after 3 - 7 days intervals, then if needed, increase to 600 mg/day after 7 days interval. Max: 600 mg/day			

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
	Sodium Valproate	400 mg/day in 2 divided doses. May be increased by 200 mg at 3 days interval Max: 1600 mg/day	Fatigue Loss of appetite Vomiting Dizziness	Avoid concomitant use of salicylates in children < 3 year old due to risk of liver toxicity. Monitor prothrombin time when used with warfarin.	Swallow whole, do not chew/crush.
Bisphosphonates	Pamidronate	60 - 90 mg as a single IV infusion over 2 - 4 hrs every 4 weeks	Asymptomatic hypocalcaemia, hypophosphataemia, hypomagnesaemia Flu-like symptoms Mild fever Local injection site reactions Malaise Rigor	Hypersensitivity to biphosphonates. Hyperparathyroidism In renal impairment, reduce dose and increase infusion duration required. In patients with poor dental hygiene, there is higher risk of ONJ. Dental referral is advised.	Rehydrate patients with normal saline before or during treatment. Not to be given as bolus injection.
	Zoledronate Acid	4 mg as 15 min IV infusion every 3 - 4 weeks	Rise in body temperature Flu-like symptoms Headache Hypersentivity reactions Osteonecrosis of the jaw		
	Clodronate	800 - 3200 mg daily (oral) Max: 3200 mg/day	Gastrointestinal irritation	Renal dysfunction	Should not be taken within one hour before or two hours after meals.

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
Corticosteroid	Dexamethasone	Oral/ IV/SC: 8 - 16 mg daily or divided doses (initial dose), then to reduce to lowest possible dose (usually 2 mg/day)	Increased or decreased appetite Insomnia Indigestion Nervousness Myopathy Oral candidiasis Adrenal suppression	Peptic ulcer disease Concomitant NSAIDs use Liver or cardiac impairment	Should be given before 6 pm to reduce risk of insomnia. Efficacy may reduce over 2 - 4 weeks.
Laxatives	Lactulose	15 - 45 ml orally, 6 - 8-hourly	Bloating Epigastric pain Flatulence Nausea Vomiting Cramping	Hypersensitivity to lactulose products Galactosemia Patients requiring galactose free diet	May be mixed with fruit juice, water or milk. Reasonable fluid intake is required for efficacy
	Bisacodyl	5 - 10 mg orally, 1 - 2 times daily Max: 30 mg/day	Atony of colon	Appendicitis Intestinal obstruction Gastroenteritis	
	Senna	2 - 4 tablets daily in divided dose	Diarrhoea Nausea Vomiting Rectal irritation Stomach cramps Bloating	Allergies especially to tartrazine	
	Macrogol	1 - 2 sachets/day	Abdominal distension Nausea Diarrhoea	Severe inflammatory bowel disease Fructose intolerance	May interfere with absorption of other drugs if administered simultaneously (take at least 2 hours apart)
Antiemetics	Metoclopramide	10 - 20 mg, 6 - 8-hourly	Extrapyramidal reactions Dizziness Drowsiness	Epileptic patients Gastrointestinal hemorrhage	

Drug Class	Drug	Recommended Dosages	Side Effects	Cautions and Contraindications	Comments
	Haloperidol	0.5 - 3 mg single dose nocte	Extrapyramidal symptoms Dystonia Prolonged QT interval Neuroleptic malignant syndrome	Concomitant use with other psychotropic drugs and metoclopramide may increase occurrence of extrapyramidal symptoms	
	Granisetron	1 mg, 12-hourly	Constipation	Progressive ileus and/or gastric distension may be masked	Should not be used as first line Not for long term use
	Ondansetron	8 mg, 12-hourly	Headache Sensation of flushing or warmth in the head and epigastrium Constipation	Pregnancy and lactation Hepatic impairment	
	Prochlorperazine	10 - 30 mg daily in divided doses Severe nausea and vomiting: 20 mg stat, followed by 10 mg after 2 hours For prevention: 5 - 10 mg 8 - 12-hourly	Extrapyramidal symptoms Dry mouth	May increased risk of seizure with tramadol	

Source:

i. Sunthornsaj N, Fun LW, Evangelista LF et. Al (Ed). MIMS.com. 117th Edition 2009. Hong Kong; CMPMedica: 2009
ii. Thomson Reuters. Micromedex® 1.0 (Healthcare Series). Greenwood Village Thomson Reuters; 2009
iii. Malaysian Association for the Study of Pain. The Malaysian Low Back Pain Management Guidelines 1st Edition. 2009

Appendix 8

GUIDE FOR TRANSDERMAL FENTANYL USE

Important notes when using transdermal fentanyl:

- When indicated, transdermal (TD) fentanyl should only be used in patients already on stable doses of morphine or other opioids.
- TD fentanyl is contraindicated in patients with severe uncontrolled pain where rapid dose titration is required.
- When converting to TD fentanyl from 4-hourly morphine, overlap regular 4-hourly morphine for the first 12 hours after applying the patch.
- When converting to TD fentanyl from 12-hourly SR morphine or CR oxycodone, apply the patch and serve the final dose of SR morphine or CR oxycodone at the same time.
- When converting to TD fentanyl from continuous SC/IV infusion of morphine or fentanyl, continue the infusion for 12 hours after applying the patch.

When applying the patch:

- The date and time of application and/or renewal should be written on the patch.
- The underlying skin should be dry, non-inflamed, non-irradiated and with minimal body hair.
- Body hair should be clipped with scissors if necessary and NOT shaved.
- If skin is washed, use only water and DO NOT apply soap, cream or ointment on the area.
- Press the patch firmly for at least 30 seconds to ensure adherence.
- Film dressings and plaster may be applied to provide additional adherence.
- After 72 hours, remove the patch and change the site of application of new patch in order to allow the skin at the previous site to rest for three days.
- Used patches should be folded with the adhesive side inwards and discarded in clinical waste bins (in hospital) or in a dustbin at home.

Source: Twycross R, Wilcock A. Palliative Care Formulary. Third Edition. Nottingham: Paliativedrugs.com; 2007

Appendix 9

GUIDE FOR NALOXONE USE

Naloxone for iatrogenic opioid overdose:-

- Seldom necessary in palliative care setting
- Used only if life threatening overdose occurs
- NOT USED for treating drowsiness or delirium associated with opioids which is not life threatening
- IV route is preferable but SC or intramuscular can also be used
- Onset of action: 1 - 2 minutes via IV and 2 - 5 minutes via SC
- Half-life: about one hour

If opioid overdose is confirmed:-

- Respiratory rate >8/minute and arousable – "Wait and see" after withholding opioids
- Respiratory rate <8/minute and comatose or cyanosed – Treat with naloxone
  - o Dilute 400 mcg (1 ampoule) in 10 ml water
  - o Administer small boluses of 0.5 ml (20 mcg) every two minutes until respiratory rate is satisfactory
  - o Titrate dose against respiratory rate and NOT conscious level as this may result in return of severe pain or physical withdrawal
- May need further boluses after one hour and sometimes infusion in cases where overdose is associated with long acting opioids (SR tablets, transdermal fentanyl or methadone)

Caution:-

- Opioid overdose must be managed with frequent close monitoring to assess effects of withdrawal and pain, and to continue or discontinue naloxone therapy as needed
- Do not use large bolus such as "1 ampoule stat" in patients who receive opioids for chronic pain relief

Source: Twycross R, Wilcock A. Palliative Care Formulary. Third Edition. Nottingham: Paliativedrugs.com; 2007

Appendix 10

PAIN MANAGEMENT AND PALLIATIVE CARE SERVICE PROVIDERS

PAIN CLINICS		
Hospital	Tel No.	URL
Hospital Selayang, Selangor	603-61203233	http://www.hselayang.moh.gov.my
Hospital Melaka, Melaka	606-2822344	http://www.hmelaka.moh.gov.my
Hospital Sultan Ismail, Johor	607-3565000	http://www.hsi.moh.gov.my
Hospital Raja Permaisuri Bainun, Perak	605-2533333	http://www.hipoh.moh.gov.my
Hospital Raja Perempuan Zainab II, Kelantan	609-7452000	http://www.hrpz2.moh.gov.my
Hospital Tengku Ampuan Rahimah, Selangor	603-33757000	http://www.htar.moh.gov.my
Pusat Perubatan Universiti Malaya, Kuala Lumpur	603-79494422	http://www.ummc.edu.my
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur	603-91455555	http://www.ppukm.ukm.my
Hospital Universiti Sains Malaysia, Kelantan	609-7663000	http://www.medic.usm.my
PALLIATIVE CARE UNITS		
Hospital	Tel No.	URL
Hospital Selayang, Selangor	603-61203233	http://www.hselayang.moh.gov.my
Hospital Bukit Mertajam, Kedah	60-45383333	http://www.hospbm.moh.gov.my
Hospital Duchess of Kent, Sabah	6089-212111	http://www.hdok.moh.gov.my
Hospital Melaka, Melaka	606-2707653	http://www.hmelaka.moh.gov.my
Hospital Pulau Pinang, Pulau Pinang	604-2293333	http://www.hpp.moh.gov.my
Hospital Queen Elizabeth, Sabah	6088-206258	http://www.qeh.moh.gov.my
Hospital Raja Permaisuri Bainun, Perak	605-5222245	http://www.hipoh.moh.gov.my
Hospital Raja Perempuan Zainab II, Kelantan	609-7485533	http://www.hrpz2.moh.gov.my
Hospital Sultanah Aminah, Johor	607-2231666	http://www.hsajb.moh.gov.my
Hospital Sultanah Bahiyah, Kedah	60-47303333	http://www.hsbas.moh.gov.my
Hospital Sultanah Nur Zahirah, Terengganu	609-6233333	http://www.hsnzkt.moh.gov.my
Hospital Tawau, Sabah	6089-773533	http://www.htwu.moh.gov.my/
Hospital Tengku Ampuan Afzan, Pahang	609-5133333	http://www.htaa.moh.gov.my
Hospital Tuanku Ja'afar, Negeri Sembilan	606-7623333	http://www.htjs.moh.gov.my
Hospital Umum Sarawak, Sarawak	6082-208069	http://www.hus.moh.gov.my
Pusat Perubatan Universiti Malaya, Kuala Lumpur	603-79494422	http://www.ummc.edu.my
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur	603-91455555	http://www.ppukm.ukm.my

HOSPICES/PALLIATIVE CARE SOCIETIES

SOCIETY	Tel No.	URL/E-mail
Hospis Malaysia	603-91333936	http://www.hospismalaysia.org info@hospismalaysia.org
Malaysian Hospice Council	604-2284140	http://www.malaysianhospicecouncil.org ncsmpg@gmail.com
Charis Hospice	604-8266757	http://www.charishospice.com charisp@streamyx.com
Home Care Hospice Programme Sabah	6088-222315	http://www.sabah.org.my/scss/cancer cancer_sabah@yahoo.com
Hospice Klang	603-33242125	http://www.hospiceklang.org hpsklang@gmail.com
Hospice Malacca	606-2925849	drrajagopal@hotmail.com
Hospice Pahang	609 5670743	-
Kasih Hospice	603-79607424	http://www.kasih-hospice.org admin@kasih-hospice.org
Kuching Hospice Cancer Care	6082-337689	cancercare@pd.jaring.my
Palliative Care Association Johor Bahru	607-2228858	pcajb.admin@gmail.com
Palliative Care Association of Kota Kinabalu Sabah	6088-231505	http://www.sabah.org.my/pcakks paliatif@streamyx.com
Penang Hospice Society	604-2284140	http://www.penanghospice.org.my chanke@islandhospital.com
Perak Palliative Care Society	605-5464732	ppcs95@tm.net.my
Persatuan Hospis Kedah	604-7332775	sriwahyu2006@yahoo.com.my
Persatuan Hospis Kelantan	609-7475418	drimisairi@kit.moh.gov.my
Persatuan Hospis Tawau	6089-774666	vicraja@gmail.com
Persatuan Hospis Terengganu	609-8593333	drahmah@trg.moh.gov.my
Pertubuhan Hospice Seremban	606-7621216	hospiceseremban_2008@yahoo.com
Pure Lotus Hospice of Compassion	604-2295481	plotus@streamyx.com
Rumah Hospis Pulau Pinang	604-2284140	http://www.penanghospice.org.my ncsmpg@gmail.com
Sarawak Hospice Society	6082-276575	tangtiengswee@gmail.com
Taiping Palliative Society	605-8072457	veraliew@hotmail.com
The Hospice Association of Sandakan	6089-632219	http://www.hospicesdk.com hcs98@hospicesdk.com

Source:

i. Malaysian Association For the Study of Pain, 2010 (internet communication, 6 February 2010 at http://masp.org.my)

ii. Hospis Malaysia, 2010 (internet communication, 6 February 2010 at http://www.hospismalaysia.org/index.php?mid=385)

iii. Asia Pacific Hospice Palliative Care Network, 2010 (internet communication, 6 February 2010 at http://www.aphn.org)

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ATC	"around the clock"
BPI	Brief Pain Inventory
CI	Confidence Interval
CNS	Central Nervous System
CPG	Clinical Practice Guidelines
CR	Controlled-release
DT	Distress Thermometer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
FLACC	Face Legs Activity Cry Consolability
HADS	Hospital Anxiety and Depression Scale
IR	Immediate-release
IV	Intravenous
MOH	Ministry of Health
NMDA	N-Methyl-D-Aspartate
NGO	Non-governmental Organisation
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ONJ	Osteonecrosis of the Jaw
OR	Odds Ratio
OTFC	Oral Transmucosal Fentanyl Citrate
PS	Pain Score
RCT(s)	Randomised Controlled Trial(s)
RR	Relative Risk
SC	Subcutaneous
SF-MPQ	Short Form McGill Pain Questionnaire
SR	Sustained-release
SNRI	Serotonin Noradrenalin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TD	Transdermal
Tmax	Time to maximum serum levels after consumption
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
VS	Versus
WHO	World Health Organization
WMD	Weighted Mean Difference

PROPOSED CLINICAL AUDIT INDICATORS FOR QUALITY MANAGEMENT

- Percentage of patients with satisfactory cancer pain control = $\frac{\text{Number of patients whose pain is satisfactorily controlled within 72 hours}}{\text{Total number of patients presenting with cancer pain}} \times 100\%$

- Annual consumption of strong opioid in Malaysia = $\frac{\text{Defined daily dose (DDD)}}{\text{100,000 population}} \times 100\%$

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