2023

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CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF CANCER PAIN

(SECOND EDITION)

Ministry of Health Malaysia

Malaysian Association for the Study of Pain

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice based on the best available evidence at the time of development. The guideline should not override the practitioners' responsibility to make decisions appropriate to the individual's circumstances. This should be done in consultation with the patients and their families or guardians, taking into account the management

options available locally.

UPDATING THE CPG

These guidelines were issued in 2023 and will be reviewed in a minimum period of four years (2027) or sooner if necessary. When it is due for updating, the Chairman of the CPG or National Advisor of the related speciality will be informed. A discussion will be done on the need for a revision, including the revised CPG's scope. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG Development Group (DG).
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "should" being considered. Otherwise, weak recommendations use the word "may" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The CPG Development Group highlighted the following recommendations as the key clinical recommendations that should be prioritised for implementation.

Cancer Pain in Adults

- **Diagnosis and Assessment**

- Accurate and comprehensive assessment should be performed prior to treatment in all patients with cancer pain.
- Appropriate pain assessment tools should be used regularly on patients with cancer pain and documented accordingly.
  - The preferred unidimensional tools are the Visual Analogue Scale, Numerical Rating Scale, Verbal Rating Scale and Faces Pain Scale.

- **Pharmacological Intervention**

- The treatment of cancer pain should be based on the World Health Organization (WHO) analgesic ladder.
- Paracetamol or nonsteroidal anti-inflammatory drugs may be used for mild cancer pain (Step 1 of the World Health Organization analgesic ladder).
- Weak opioids may be used for moderate pain (step 2 of the WHO analgesic ladder) in cancer pain.
- Oral morphine is the preferred choice in moderate to severe cancer pain.
  - Immediate-release oral morphine should be made available in all healthcare facilities.
- Oxycodone and fentanyl can be used as alternatives to morphine.
- Transdermal fentanyl should only be used when opioid requirements are stable.
- Patients with persistent cancer pain should be prescribed with regular (around-the-clock) analgesia.
  - Opioid doses must be titrated to achieve optimal pain relief with minimal adverse events.
  - Long-acting opioid formulations may be considered for patients once the effective opioid dose has been established.
- All patients with cancer pain who are on opioids should be prescribed with rescue analgesia if required to ensure optimal pain control.

- Opioids (morphine or oxycodone) for breakthrough cancer pain should be prescribed at 1/6 to 1/12 of the 24-hour dose.
- In the management of cancer pain for older patients or those with renal/liver impairment:
  - All opioids should be used with caution.
  - Adjustment in doses/frequency of opioids should be considered.
- Opioid-induced side effects should be proactively identified and treated adequately to ensure optimum cancer pain management.
- Anticonvulsants or antidepressants may be considered in patients with neuropathic cancer pain.
- Corticosteroids may be used cautiously as an adjuvant in patients with specific cancer pain syndromes.
- Bone targeting agents may be used in cancer patients with painful bone metastasis.
- Radiotherapy may be offered to control pain in symptomatic bone metastasis.
  - Single-fraction external beam therapy is the preferred choice.
- Psychoeducation, psychological and spiritual interventions should be considered in the management of cancer pain.
- Patients whose pain control is poor despite optimal pharmacological therapy should be referred to specialists trained in interventional pain management for consideration of the following interventions:
  - coeliac plexus neurolysis for advanced pancreatic cancer pain
  - superior hypogastric plexus or ganglion impar neurolysis for advanced pelvic and perineal cancer pain
  - intrathecal drug delivery system
  - vertebroplasty for malignant spinal compression fractures

Cancer Pain in Children

- Paracetamol or nonsteroidal anti-inflammatory drugs should be used in children with mild cancer pain.
- Paracetamol should be used in combination with opioids as co-analgesic unless contraindicated in children with cancer pain.
- Oral morphine is the preferred choice for children with moderate to severe cancer pain.
- Fentanyl or oxycodone may be used as alternative analgesics in children with moderate to severe cancer pain.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the DG for this CPG were from the Ministry of Health (MoH) and the Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee during the process of the CPG development.

A systematic literature search was conducted using the following electronic databases/platforms: Medline via Ovid and Embase. Refer to **Appendix 1** for an **Example of Search Strategy**. The inclusion criteria are cancer patients with pain regardless of study design. The first search was limited to literature published in the last 13 years (2010 until 2023) for most clinical questions on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field were contacted to identify relevant studies. All searches were conducted from 21 February 2022 to 21 October 2022. The literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 June 2023 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines on cancer pain as listed below:

- World Health Organization (WHO) Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents 2018
- Management of Cancer Pain in Adult Patients: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines 2018
- European Society for Medical Oncology (ESMO) Clinical Practice Guidelines in Oncology - Adult Cancer Pain 2019
- Use of Opioids for Adults with Pain from Cancer or Cancer Treatment: American Society of Clinical Oncology (ASCO) Guideline 2023
- Paediatric Pain Management Guidelines 2023
- The Children's Hospital at Westmead Pain Management Practice Guideline 2021
- The University of Texas MD Anderson Cancer Center Cancer Pain - Pediatric (Age ≤18 Years) 2021
- Handbook of Children's Palliative Care Malaysia 2021
- Latin-American guidelines for cancer pain management 2017
- CRIS Cancer Clinical Practice Guideline for Pain Management in Children with Cancer 2013

- WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illness 2012

A total of 23 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 24 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using the Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and recommendations formulated after that were agreed upon by both the DG and the review committee (RC). Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. The CPG was mainly based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices considered.

The literature used in these guidelines was graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001) while the recommendation grading was done using GRADE principles (refer to the preceding page). The writing of the CPG follows strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE II).

On completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from the **Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015** (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPG are to provide evidence-based guidelines to optimise pain control with minimal side effects and adverse outcomes, enhance well-being and improve the quality of life (QoL) of patients with cancer pain.

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- Adults and children of all ages with pain from any type of cancer

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in primary and secondary/tertiary care of the management of cancer pain including:

- doctors
- allied health professionals
- trainees and medical students
- policymakers
- patients and their advocates
- professional societies

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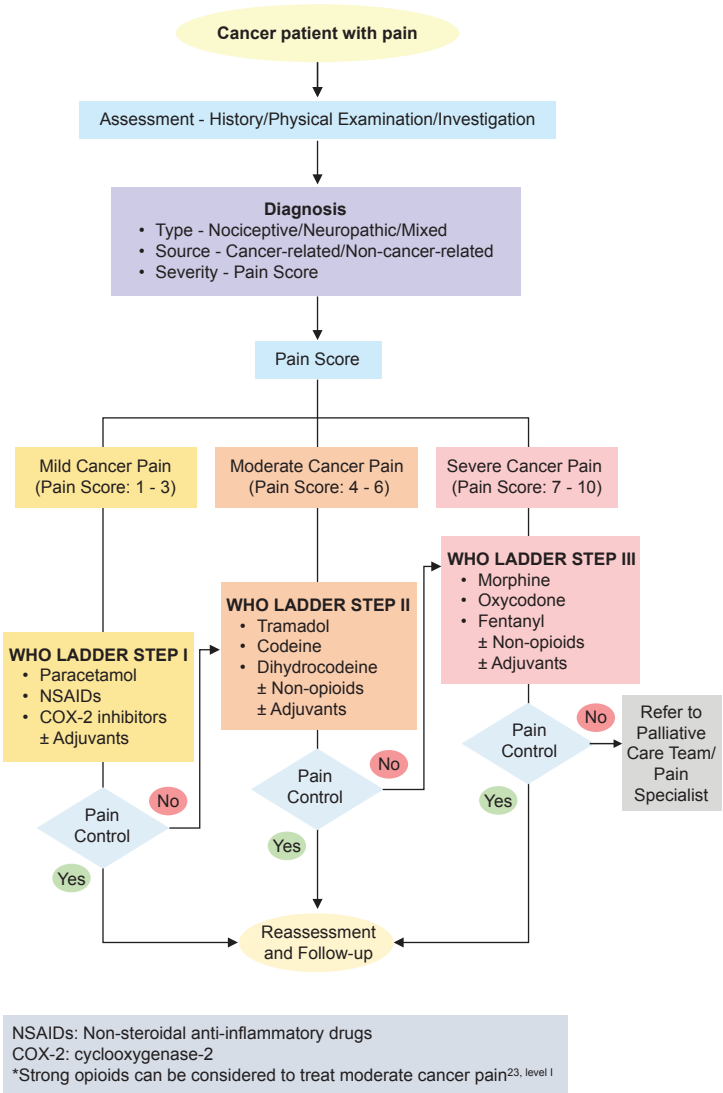
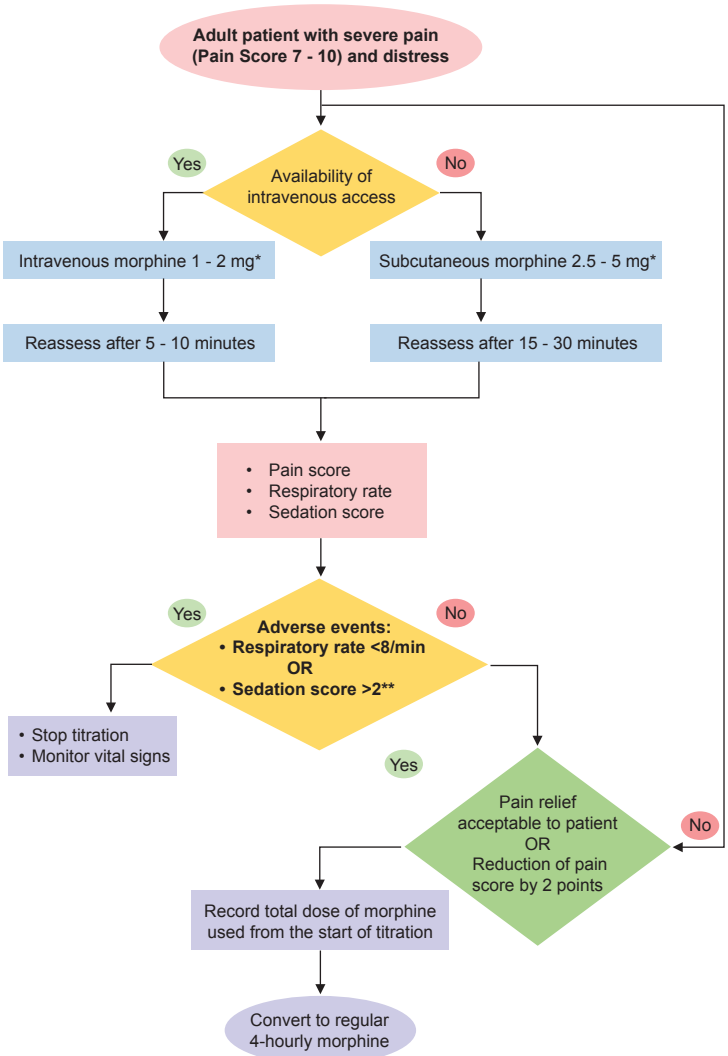
ALGORITHM 1. MANAGEMENT OF CANCER PAIN IN ADULTS



NSAIDs: Non-steroidal anti-inflammatory drugs
COX-2: cyclooxygenase-2
*Strong opioids can be considered to treat moderate cancer pain[23, level I]

Adapted: Ministry of Health, Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

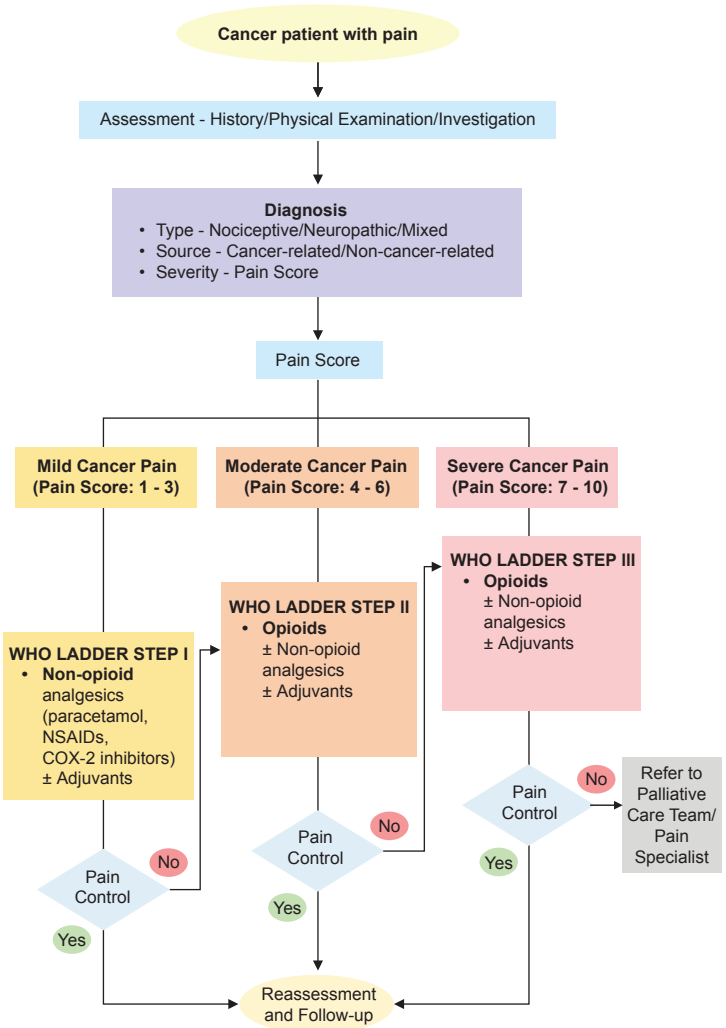
ALGORITHM 2. TITRATION OF MORPHINE FOR RAPID PAIN RELIEF IN ADULTS WITH SEVERE PAIN AND DISTRESS



*For patients already on opioids, the bolus dose of morphine should be 10% of the total 24-hour morphine requirement converted to intravenous/subcutaneous equivalent. For elderly, frail or renal impaired patients, use lower dose of the given range.
For details on sedation score, see **Appendix 3 in the CPG.

Adapted: Ministry of Health, Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

ALGORITHM 3. MANAGEMENT OF CANCER PAIN IN CHILDREN



1. INTRODUCTION

World Health Organization (WHO) reported that there were 48,639 new cancer cases in Malaysia in 2020.[1] Cancer accounted for over 10% of all medically-certified deaths in the country in 2021.[2] For those living with cancer, pain is a common and distressing symptom that affects their quality of life.

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[3] Cancer pain or cancer-related pain is pain experienced by patients with cancer due to cancer itself or its treatment. A large meta-analysis showed prevalence rates of cancer pain at 39.3% after curative treatment, 55.0% during anticancer treatment and 66.4% in advanced, metastatic or terminal disease. Moderate to severe pain (numerical rating scale score ≥5) was reported by 38.0% of all patients.[4, level III] This indicates that cancer pain is still prevalent despite treatment and about a third of the patients suffer from more than just mild pain. There is no local data on the prevalence of cancer pain. However, a local study found that recognition of cancer symptoms which included pain was relatively low across Malaysia.[5, level III]

The consumption of strong opioid analgesics (morphine, oxycodone, fentanyl etc.), which are essential for managing moderate to severe cancer pain, is relatively low in Malaysia compared with other countries. A recent local study found that the total strong opioid consumption (excluding methadone) in Malaysia was 0.086 defined daily doses (DDD) per 1000 inhabitants per day in 2005, which increased to 0.126 DDD in 2014. However, this was lower than the global average of 32.8 DDD/1000 inhabitants/day.[6, level III]

The main barriers to effective pain control in Malaysia relate to physicians' and patients' attitudes towards the use of opioids. In one survey among physicians, 46% felt they lacked the knowledge to manage patients with severe pain, 40% were concerned about opioid addiction and 38% were worried about legal issues. In a survey of patients, 62% reported that they did not want to take opioids because they believed that opioids were only for terminal cases, 54% feared adverse effects (AEs) e.g. constipation and nausea and 48% feared becoming addicted.[7, level III] These misconceptions and fears may prevent patients from reporting their pain or requesting opioids, and physicians from prescribing adequate doses or using appropriate routes of administration.

The first edition of CPG in cancer pain management in Malaysia has helped to spearhead the improvement in this field. Since then, services that provide cancer pain management increased in hospital,

primary care and community hospice levels. This updated CPG aims to expand the information and incorporate new and current evidence of pharmacological/non-pharmacological management in cancer pain.

2. PRINCIPLES OF MANAGEMENT

- The guiding principles of cancer pain management are:[8, level I; 9; 10, level I]
  - a comprehensive pain assessment
  - the application of the concept of Total Pain
  - the involvement of a multidisciplinary team
  - an emphasis on patient and family-centred care
  - the individualisation of the pain experience and response

The principles of cancer pain management have remained similar over the years and their importance has been strengthened by research. A systematic review has reaffirmed the core principles outlined in the first edition of the Malaysian CPG on Management of Cancer Pain.[10, level I]

Comprehensive cancer pain assessment remains the first and foremost principle in providing good cancer pain management.[9] A detailed history, physical examination, psychological assessment, suitable pain measurement tools and appropriate diagnostic procedures are components of a good assessment. Regular reassessment is vital to ensure that treatment is effective and safe.[11]

Cancer pain assessment is further enhanced by the concept of Total Pain (refer to **Figure 1**) which guides healthcare providers to view the multidimensionality of pain. A holistic review of the physical, psychological, social and spiritual aspects would provide a better understanding of the individual's experience of pain.[8, level I]

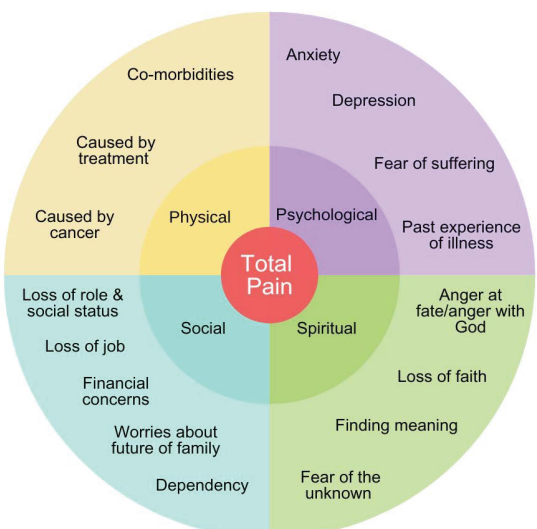


Figure 1. Concept of Total Pain

Source: Franklin AE, Lovell MR. Pain and Pain Management. In: Roderick Duncan MacLeod, Lieve Van den Block, editors. Textbook of Palliative Care. Cham: Springer International Publishing; 2018. p. 1-29.

A multidisciplinary team is often required to address the many needs of a patient. A team comprising healthcare professionals of different expertise may be able to provide effective and comprehensive pain relief through various treatment methods.[8, level I] The core team should consist of a physician, nurse, pharmacist, clinical psychologist, social worker, physiotherapist, occupational therapist and spiritual care provider. Other healthcare providers may be included based on the patient's needs. High-intensity interprofessional collaboration in managing cancer pain has shown:[9]

- improvement in mean patient satisfaction
- less uncertainty and concerns among patients
- adequacy in pain management

A cohort study showed that a multidisciplinary palliative care team significantly reduced pain intensity and other symptoms in cancer patients.[12, level II-2] Another study on the impact of a clinical pharmacist-led team showed that it improved standardisation of opioid administration, pain scores and quality of life, and reduced gastrointestinal (GI) AEs compared with usual care in cancer pain.[13, level II-1]

Healthcare providers should involve the patient and their family/caregiver to understand the patient's values and preferences when planning their cancer pain treatment. Good communication and collaboration with the patient and their family/caregiver during decision-making will ensure optimal care is provided in the patient's best interest.[10, level I] Furthermore, the involvement of patients and their family/caregiver in managing cancer pain reduces barriers to analgesic use and decreases the worst pain score.[9]

Healthcare providers should be aware that the patient's experience and response to pain is highly individualised. There are many factors that influence an individual's response to pain e.g. age, cognitive abilities, cultural background and previous experience of pain. Recognising this may help in providing individualised care and alleviating pain more effectively.[10, 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. 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.[9]

Assessment of pain is a vital step in cancer pain management and is the responsibility of all healthcare providers. Accurate and comprehensive assessment should be performed prior to treatment to plan for appropriate interventions and to assess their effectiveness after initiation.[9]

- Pain assessment aims to determine the:
  - nature and pathophysiology of pain
  - severity of pain
  - impact of pain on functions and quality of life
  - response to interventions

Like other clinical assessments, a complete pain assessment requires a detailed history, physical examination and relevant investigations.

3.1 Clinical Presentation

Cancer pain can be classified by various methods according to aetiology, pathophysiology, anatomical location of pain syndrome, temporal pattern and severity. In the clinical context, cancer pain is often described using a combination of these classifications. Clinical characteristics of the pathophysiological 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 ○ Subdivided into somatic and visceral types based on the nature of tissue injury
• Somatic Pain	▪ Damage of somatic tissue such as bones and soft tissue ▪ Character is aching, stabbing or throbbing ▪ Pain is usually well localised ▪ Often made worse by movement

• Visceral pain	▪ Damage is to viscera e.g. liver, intestines, pancreas, bladder, etc ▪ Character is cramping or gnawing when due to obstruction of hollow viscus ▪ Character is aching, sharp or throbbing due to tumour involvement of organ capsule ▪ Pain is usually diffuse and difficult to localise ▪ Pain may be referred to somatic structures
Neuropathic Pain	○ Pain is due to abnormal somatosensory processing in the peripheral or central nervous system ○ 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 (pain due to a stimulus that does not normally provoke pain) or dysaesthesia (sponta-neous or touch-evoked unpleasant sensations), may be present

Source: Ministry of Health Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

Knowledge about pain characteristics, syndromes and pathophysiology provides a useful background to understand cancer pain and helps to determine appropriate interventions. Cancer patients experience pain due to the underlying cancer or from its treatment. However, not all pain experienced is from the cancer itself, it could sometimes be due to pre-existing conditions. This emphasises the need to assess and differentiate benign causes of pain (e.g. osteoarthritis, migraine and osteoporosis) which may be managed differently from cancer pain.[9]

List of Common Pain Syndromes:[9]

- Nociceptive syndromes related to direct tumour involvement
  - Base of skull metastasis
  - Vertebral syndrome
  - Diffuse or multifocal bone pain
  - Pain due to neoplastic involvement of viscera e.g. 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

3.2.1 History Taking

Taking a good pain history is important for accurate clinical assessment as most pain diagnoses can be made based on history alone.

Table 2. Points for History Taking

Characteristics of pain	• Site(s) - 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/targeted therapy
Medication	• Analgesics and adjuvants • 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-spiritual	• Emotional/psychological - depression/ anxiety/stress, etc. • Meaning of pain to the patient • Effects on activities of daily living/appetite/sleep • Effects on socio-economic functioning • Perception of pain and pain medications

Source: Ministry of Health Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

3.2.2 Physical Examination

After taking a full history, physical examination serves to confirm the clinical diagnosis. This helps to provide a comprehensive understanding of the patient's condition and extent of problems.

3.2.3 Investigations

Investigations may be necessary to support the diagnosis and/or assist clinical decision-making in certain conditions. These may include radiological investigations such as plain X-rays, bone scans, computerised tomography (CT) scans and magnetic resonance imaging (MRI), and blood investigations e.g., liver and renal function tests. Investigations should be ordered only if the results could potentially influence clinical management.

3.3 Pain Assessment Tools

Effective pain management requires careful assessment and documentation of the pain. Pain assessment tools incorporate unidimensional and multidimensional measures. The most commonly used unidimensional assessment tools which are validated and adequately reliable are:

- Visual Analogue Scale (VAS)
- Numerical Rating Scale (NRS)
- Verbal Rating Scale (VRS)
- Faces Pain Scale (FPS)

It is crucial to determine suitable assessment tools for each patient according to his/her ability to use the tools. The scores should be carefully interpreted by healthcare providers. Pain assessment using a unidimensional scale is easily executed (with minimal training) and sustainable in outpatient settings. In the implementation of "Pain as the 5th Vital Sign", MoH has advocated the pain assessment tools as listed in **Appendix 4a** (MoH Pain Scale) & **4c** (VRS).[14]

A correlational study on various unidimensional tools [(NRS-11), Faces Pain Scale (FPS), Verbal Descriptor Scale (VDS) and a mixed scale (consisting of NRS-11, FPS and VDS)] in cancer patients aged ≥65 years showed:[15, level III]

- all four scales were reliable and valid for assessing cancer pain
- NRS-11 had the highest test-retest reliability for current pain
- VDS had the highest reliability for least pain
- FPS had the highest reliability for average pain
- mixed scale had the highest reliability for worst pain

A large systematic review measured assessment tools (unidimensional and multidimensional) for cancer pain in adults based on psychometric properties and clinical utility. The highly recommended tools were:[16, level III]

- McGill Pain Questionnaire (MPQ)-Short Form
- NRS
- VAS

The other four recommended tools were Brief Pain Inventory (BPI), BPI-Short Form, MPQ and Pain Disability Index. However, there was no mention on the quality of the primary papers used in the review.

Recommendation 1
- Accurate and comprehensive assessment should be performed prior to treatment in all patients with cancer pain.
- Appropriate pain assessment tools* should be used regularly on patients with cancer pain and documented accordingly.
  - The preferred unidimensional tools are Visual Analogue Scale, Numerical Rating Scale, Verbal Rating Scale and Faces Pain Scale.

*Refer to **Appendix 4** for **Assessment Tools**

3.3.1 Assessment tools for neuropathic pain

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system".[3] It is a frequent consequence of cancer pain and poses considerable suffering to the patients and their families.

Neuropathic pain is a notable clinical challenge in relation to diagnosis and thus can be overlooked in cancer pain. A cross-sectional study looked into the predictors and common symptoms of neuropathic cancer pain and showed:[17, level III]
- predictors were age <65 years old, disease duration >6 months, stage IV cancer, history of chemotherapy and moderate-to-severe cancer pain
- common descriptive symptoms were tingling, electric shock, and 'pins and needles'

It is important to identify neuropathic pain using appropriate tools. Two diagnostic studies looked into the accuracy of such tools. The first study on The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale compared pain of predominantly neuropathic or nociceptive origin in patients with refractory cancer-related pain. Based on the reference test of clinician assessment, the AUC was 0.96 and a specificity of 100% at a cut-off value of 12 points in detecting neuropathic pain.[18, level I]

In another diagnostic study on neuropathic pain in oncology patients using pain specialist's diagnosis as the gold standard, the findings were:[19, level III]
- AUC of PainDETECT and Doeleur Neuropathique en 4 (DN4) were 0.870 (95% CI 0.813 to 0.926) and 0.857 (95% CI 0.799 to 0.914) respectively

- PainDETECT had a specificity of 100% at cut-off value of ≥19, while DN4 had 88.7% with a cut-off value of ≥4

- The following tools have shown good diagnostic properties in detecting neuropathic pain:
  - LANSS
  - PainDETECT
  - DN4
- The diagnosis of neuropathic pain needs to be confirmed with clinical assessment.

3.3.2 Comprehensive Assessment

A comprehensive assessment is essential to achieve successful cancer pain management. It includes the elements of history taking, physical examination, psychological and spiritual assessment. The use of assessment tools during clinical encounters has the potential to shape the individual patient's care in terms of experience, compliance, satisfaction and improve rapport with healthcare providers. There are a number of available tools for comprehensive assessment e.g. Integrated Palliative Care Outcome Scale (IPOS), Edmonton Symptom Assessment System (ESAS) and Memorial Symptom Assessment Scale (MSAS).[11]

The IPOS is valid (good internal consistency with Cronbach α of 0.77) and reliable (good test-retest reliability with 60% of items having K_w >0.60) for outcome measures, both in patient self-report and staff proxy-report versions.[20, level III]

ESAS has many modified versions. A correlational study on ESAS using NRS with additional symptoms of constipation, sleep and added time window of "past 24 hours" (ESAS-CS) and a version where a time window of "now" was added (ESAS-r-CS) were compared with MSAS. The findings were:[21, level III]

- ESAS-CS and ESAS-r-CS total scores correlated moderately with total MSAS (Spearman's rho 0.62 and 0.64 respectively)
- although participants preferred the ESAS-r-CS format (42.8% vs 18.6%) because of greater clarity and understandability, the ''past 24 hours'' time window (52.8%) was favoured over ''now'' (21.3%)
- shortness of breath and nausea correlated better for the ''past 24 hours'' time window (0.8 and 0.72 vs 0.74 and 0.64 in ESAS-CS and ESAS-r-CS respectively)
- the 24-hour test-retest of the ESAS-CS demonstrated acceptable reliability (ICC=0.69)

For psychological assessment, the screening tools to measure and recognise distress have to be simple and practical. There are the single-item Distress Thermometer (DT) (refer to **Appendix 4h & 4i**) and the multiple-item tools such as Hospital Anxiety and Depression Scale (HADS), Brief Symptom Inventory-18 (BSI-18),[9] Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) that are used to screen for psychological distress.

The foundation for spiritual evaluation models is a collection of interpretive frameworks that requires substantial training in its use. The common tools used in spiritual assessment are the FICA Spiritual History Tool and HOPE Spiritual Assessment Tool.

- IPOS and ESAS are examples of comprehensive assessment tools for patients with cancer pain.
- DT and HADS are some psychological assessment tools used to screen for psychological distress.

3.3.3 Pain assessment tools in cognitive impairment/learning disability

Pain assessment in patients with cognitive impairment is challenging as self-reported assessment tools are inaccurate. Hence, observational tools e.g. the Face Legs Activity Cry Consolability (FLACC) scale and The Pain Assessment in Advanced Dementia tool (PAINAD) may be helpful.

The PAINAD is one of the tools mentioned in WHO guidelines to assess pain in patients with advanced dementia.[11] A study evaluating the psychometric properties of the PAINAD scale in medical inpatients with dementia showed good inter-rater reliability (ICC of 0.92 at rest and 0.98 in movement) and internal consistency (Cronbach's α of 0.76 at rest and 0.80 in movement).[22, level III]

The MoH guidelines on Pain as the 5th Vital Sign states that FLACC scale can be used for cognitively impaired adults.[14, level III]

- Observational tools e.g. FLACC scale or PAINAD may be useful to assess pain in cognitively impaired adults.

4. PHARMACOLOGICAL INTERVENTION

The cornerstone of cancer pain management is using pharmacological agents to provide pain relief and improve the quality of life for the patients. The analgesics used can be divided into three main classes, namely opioids, non-opioids and adjuvant medications. The choice of analgesic as well as the dose and route of administration would depend on the type and severity of pain. Other factors to be considered include age, co-morbidities and patient's adherence. A combination of medications may be used. It is essential to monitor the patient's response to the medication while minimising any AEs in achieving optimal pain control.

4.1 Principles of Analgesic Medicine

WHO recommends the use of analgesic medicine should follow these principles:[11]

- By mouth
  - Analgesic medication should be given by mouth whenever possible.
- By the clock
  - Doses of analgesic medication should be given at fixed intervals around-the-clock.
  - The aim is for the next dose to be given before the previous dose effect has worn off.
- For the individual
  - As each patient is unique and different, analgesic therapy should be individualised.
  - This is based on the type of pain, response to medication, AE etc.
- Attention to detail
  - Prescription timing should consider the patient's day and sleep schedule.
  - Education on the use of these medications should be given including effects and AEs.

4.2 World Health Organization Analgesic Ladder

The 3-step World Health Organization (WHO) analgesic ladder, which was introduced in 1986, remains useful as an educational tool but not as a strict protocol for cancer pain treatment.[11]

The WHO analgesic ladder as shown in **Figure 2** consists of three steps: Step 1 for a pain score of 1 - 3 (mild), step 2 for a pain score of 4 - 6 (moderate) and Step 3 for a pain score of 7 - 10 (severe). The choice of analgesia is based on the intensity of pain.

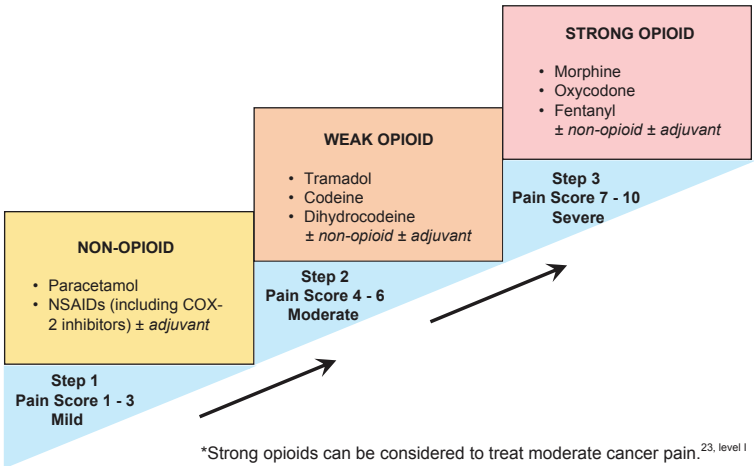


Figure 2. WHO Analgesic Ladder

Adapted: Ministry of Health, Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

A multi-centre RCT showed that low doses of morphine were more effective than standard doses of weak opioids for moderate cancer pain in opioid-naive patients as shown below:[23, level I]

- 88.2% of patients on morphine and 54.7% of patients on weak opioids achieved pain reduction of ≥20% from baseline (OR=6.18, 95% CI 3.12 to 12.24)
- the effectiveness of morphine over weak opioids was evident in the first week after initiation of treatment (80.9% vs 43.6%; p<0.001) and remained constant over four weeks

Both drug treatments were well tolerated with no differences observed in the intensity and frequency of opioid-related side-effects between them.

In a recent pragmatic clinical trial, there was some evidence that a 2-step approach was an alternative option and may be less expensive than a 3-step approach in cancer pain management. However, the findings of this trial were not intended to negate or advise against the use of the original ladder and should be regarded as explorative as this study was underpowered.[24, level I]

Recommendation 2

- The treatment of cancer pain should be based on the World Health Organization (WHO) analgesic ladder.

4.3 Non-opioids

A systematic review of 12 clinical trials comparing nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol added to WHO Step III opioids and opioids alone in moderate to severe cancer pain showed the following findings:[25, level I]

- NSAIDs added to opioids
  - Five of seven studies showed a positive impact where three demonstrated improved analgesia and two showed a reduction in opioid consumption.
  - In terms of safety, six studies failed to demonstrate any statistically significant difference between the two groups. In contrast, one study showed that constipation was significantly more frequent in the morphine group and gastric discomfort was significantly more frequent in the morphine and ketorolac group.
- Paracetamol added to opioids
  - Four studies failed to confirm any benefit of add-on paracetamol treatment. In contrast, one study reported a slightly greater reduction in pain score for paracetamol combination [MD of 0.4 on a 0 - 10 numeric rating scale (NRS)]. This study used the highest paracetamol dose (5 g/day) and had a short follow-up (96 hours).
  - AEs were similar between the groups except for one study in which increased somnolence was present in patients on methadone plus paracetamol.

The quality assessment of the primary papers was not well reported.

A Cochrane systematic review on oral NSAIDs for cancer pain in adults found:[26, level I]

- no high-quality evidence to support or refute the use of NSAIDs alone or in combination with opioids for the three steps of the WHO cancer pain ladder
- very low-quality evidence that some people with moderate or severe cancer pain can obtain substantial levels of benefit within one or two weeks

Another Cochrane systematic review on the effectiveness and safety of paracetamol in cancer pain revealed:[27, level I]

- no convincing evidence of paracetamol being different from placebo with regards to QoL, use of rescue medication and participants' satisfaction or preference
- measures of harm (serious AEs and other AEs) were inconsistently reported and provided no clear evidence of difference between the groups

- There is no high-quality evidence to support the use of paracetamol or NSAIDs as an add-on to opioid analgesia in cancer pain.

While the previous edition of CPG on Management of Cancer Pain, paracetamol or NSAIDs are the drugs of choice for mild cancer pain (Step 1 of the WHO analgesic ladder).[9] WHO guidelines for cancer pain recommends that NSAIDs, paracetamol or opioids should be used at the stage of initiation of pain management, either alone or in combination in adults and adolescents with pain related to cancer. This depends on the clinical assessment and pain severity of the patients.[11]

Recommendation 3
- Paracetamol or nonsteroidal anti-inflammatory drugs may be used for mild cancer pain (Step 1 of the World Health Organization analgesic ladder).

4.4 Opioids

Opioid analgesics are essential for the treatment of moderate to severe cancer pain. Constipation, nausea, vomiting, drowsiness and pruritus are common AEs of opioids.

4.4.1 Weak opioids

Weak opioids which include tramadol, dihydrocodeine and codeine are also classified as WHO step-2 ladder opioids and mainly used for mild to moderate cancer pain.[28]

Tramadol acts both as a central opiate agonist and central nervous system reuptake inhibitor of norepinephrine and serotonin. Liver or renal impairment may require dose adjustments because of tramadol hepatic metabolism and renal clearance. Serotonin syndrome has been reported with the use of tramadol especially with concurrent use of other serotonergic drugs e.g. antidepressants.[29, level III]

The use of tramadol is prevalent in cancer pain management although data on its use is not extensive. In a Cochrane systematic review on moderate to severe cancer pain, tramadol exhibited lower effectiveness compared with morphine based on very low-quality evidence. Tramadol doses ranged from 50 - 600 mg/day with the most common dose being 300 - 400 mg/day in line with the usual clinical practice. Comparisons between tramadol and dihydrocodeine did not yield any significant information. Most of the results in this review came from an RCT in 2016 comparing weak opioids with low-dose morphine with the latter having a higher percentage of patients achieving a reduction in pain

of ≥30% (OR=5.4, 95% CI 2.92 to 9.97) and ≥50% (OR=4.27, 95% CI 2.42 to 7.54).[30, level I]

Tramadol exhibits the typical opioid AEs of nausea, dizziness and dry mouth. There is also an increased risk of convulsion with its use. However, vomiting and constipation is expected to be less compared with strong opioids.[29, level III]

A Cochrane systematic review comparing codeine ± paracetamol with placebo found limited evidence to indicate that codeine is more effective in cancer pain. However, it had an increased risk of nausea, vomiting and constipation.[31, level I] In clinical practice, oral codeine and dihydrocodeine appear to be equipotent.[9]

Weak opioids are generally more accessible compared with strong opioids. In situations where access to morphine or other strong opioids may be limited or not immediate, tramadol or dihydrocodeine may be an option in cancer pain management.

Recommendation 4
- Weak opioids may be used for moderate pain (step 2 of the WHO analgesic ladder) in cancer pain.

4.4.2 Strong opioids

Strong opioids commonly used in Malaysia include morphine, fentanyl and oxycodone. They are recommended for use in moderate to severe cancer pain. There is no maximum dose for this group of opioids and the appropriate dose is the dose which provides pain relief without causing major or intolerable AEs. In most settings, morphine remains the first choice for reasons of familiarity, availability and cost.[28] It is also listed in the WHO essential medicines list.[32]

- **Morphine**

A large Cochrane systematic review of 62 studies compared the effectiveness and safety of oral morphine with various controls in relieving cancer pain. The range of oral morphine doses used varied from 25 mg/day to 300 mg/day and titrated to effect. Mean daily doses ranged from 100 mg/day to 250 mg/day with the maximum dose recorded at 2000 mg/day. The findings were:[33, level I]

  - morphine was an effective analgesic for moderate to severe cancer pain and >90% of participants had 'no worse than mild pain'
  - adverse events (AEs) were common and predictable but only approximately 6% of participants discontinued treatment with morphine because of intolerable AEs

Other results of the above review were:

- oral morphine was as effective as other opioids when used at the correct dose as no conclusive evidence was found on other strong opioids being superior in effectiveness to morphine
- no difference in pain relief between immediate-release (IR) and sustained-release (SR) morphine
- no conclusive evidence on the effectiveness of double bedtime dose of IR morphine to improve pain relief and prevent the patients receiving 4-hourly dosing from being woken up at night

The quality of the evidence was generally poor with some studies being old, small and designed for registration purposes.

In the previous edition of CPG on cancer pain, it is stated that oral morphine should be the first choice of treatment in moderate to severe cancer pain. Alternatives to it are oxycodone and fentanyl.[9]

WHO recommends oral morphine, i.e. regular dosing of IR or SR formulation, should be used to maintain effective and safe pain relief in cancer pain. IR morphine should be used as rescue medicine with either formulation. Thus, IR morphine must be available and accessible to those who require it. Apart from that, SR morphine should be made available as an addition to IR morphine.[11]

The time to peak plasma concentration (Tmax) of IR and SR oral morphine is 1 hour and 2 - 6 hours respectively. The Tmax for intravenous (IV) and subcutaneous (SC) morphine is 5 - 10 minutes and 15 minutes respectively. The duration of action of IR and SR morphine is 3 - 6 hours and 12 hours respectively.[34]

- **Oxycodone**

Oxycodone is an alternative strong opioid which is available in IR and CR oral formulations. A recent Cochrane review on adult cancer pain found that there was little to no difference in pain intensity, pain relief and AEs between oxycodone and other strong opioids including morphine. The review also found that constipation and hallucinations occurred less often with CR oxycodone than with CR morphine ([RR of 0.75 (95% CI 0.66 to 0.86) and 0.52 (95% CI 0.28 to 0.97 respectively)]. However, these two findings should be treated with caution as the certainty of the evidence was either very low or unstable with sensitivity analysis.[35, level I]

IR oxycodone has a Tmax of 1 - 1.5 hours and a plasma half-life of 2 - 4 hours.[34] The CR oxycodone is absorbed in a bi-exponential fashion with a rapid phase half-life of 37 minutes (accounting for 38% of the dose) and a slow phase half-life of 6.2 hours (which accounts for the residual 62%). This allows the onset of analgesia using CR

oxycodone within one hour of ingestion and an analgesic duration of 12 hours.[36, level III]

- **Fentanyl**

Fentanyl is an alternative opioid that can be used in cancer pain. In Malaysia, it is available as transdermal patch, sublingual and parenteral preparations.

Transdermal (TD) fentanyl should only be considered in patients with stable opioid requirements who have difficulty swallowing or intractable nausea and vomiting.[9] In a Cochrane systematic review comparing TD fentanyl with oral morphine for relief of cancer pain, there was insufficient comparable data for a meta-analysis to be undertaken for the analgesic effect. However, transdermal fentanyl showed a reduction in constipation (RR=0.61, 95% CI 0.47 to 0.78; NNT=5.5). No meaningful analysis was possible for other AEs.[37, level I]

When switching from other opioids to transdermal fentanyl, there is a lag time between application of the patch and onset of analgesia due to its pharmacokinetics whereby on average, minimally effective plasma concentrations of fentanyl are seen in 12 hours. Regular 4-hourly oral opioids should therefore, be discontinued 12 hours after patch application. Similarly, when converting from SR opioid preparations, the patch should be applied together with the last dose of SR medication.[9] However, an RCT on the conversion of IV to transdermal fentanyl in chronic cancer pain revealed that the effectiveness of continuing the IV for six hours after patch application (6-h method) was equivalent to the 12-h method in terms of number of rescue doses for breakthrough pain required ($p>0.05$) and thus may be considered for a simpler method of conversion.[38, level I]

The Tmax of transdermal fentanyl is 12 - 24 hours and the duration of action is 72 hours. The plasma half-life of transdermal fentanyl ranges from 13 - 22 hours. Parenteral fentanyl (e.g. boluses of IV/SC) has a short duration of action of approximately 60 minutes and is not routinely used for maintenance therapy.[34]

Fentanyl is generally considered a safer opioid in renal impairment as its metabolites have minimal effect.[39, level I]

The approximate pharmacokinetic parameters of morphine, oxycodone and fentanyl are shown in **Table 3**.

Table 3. Pharmacokinetic Parameters of Morphine, Oxycodone and Fentanyl

Pharmacokinetic parameters	Morphine	Oxycodone	Fentanyl
Onset of action	Oral IR: 30 mins IV: 5 mins SC: 15 mins SR: 3 hours		TD: 12 hours* IV: 1.5 mins SC: 15 mins
Time to peak concentration (Tmax)	Oral IR: 1 hour IV: 15 mins SC: 30 mins SR: 6 hours		TD: 12 - 24 hours IV: 5 mins SC: 5 - 30 mins
Half-life ($t_{1/2}$)	IR oral/IV/SC: 2 - 4 hours SR: 4 - 5 hours		TD: 13 - 22 hours IV/SC bolus: <1 hour
Duration of action	IR oral/IV/SC: 4 - 6 hours SR: 12 hours		TD: 72 hours IV/SC:1 hour

*Following the application of the first patch

Recommendation 5
- Oral morphine is the preferred choice in moderate to severe cancer pain.
  - Immediate-release oral morphine should be made available in all healthcare facilities.
- Oxycodone and fentanyl can be used as alternatives to morphine.
- Transdermal fentanyl should only be used when opioid requirements are stable.

4.4.3 Opioid initiation, titration and maintenance

- **Initiation**

Strong opioids should be initiated at the lowest effective dose. For persistent pain, an IR formulation should be given every four hours to control background pain and with similar doses given up to every hour as needed for breakthrough pain. Patients who have been taking other analgesics, such as NSAIDs, may continue these analgesics after opioid initiation if these agents provide additional analgesia and are not contraindicated.

Oral morphine is the first-line therapy for moderate to severe cancer pain. A dose of 5 mg 4-hourly of IR oral morphine in opioid-naive patients has been shown to be a safe and effective starting dose ($p<0.01$). Opioid-naive patients are those not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. Patients already on regular weak opioids (tramadol or dihydrocodeine) may have morphine initiated at a dose equivalent to that of the weak opioid (refer to **Table 4**). A lower starting dose of 2.5 mg 4 - 6 hourly of IR oral morphine has been shown to be effective ($p<0.01$) and safe in elderly or frail patients.

- **Titration**

Early assessment and dose titration must be carried out in all patients initiated on opioids. Dose titration can be done as early as 24 hours after initiation. A dose increment may be necessary when a patient reports persistent pain, or needs to take multiple doses for breakthrough pain (>3 doses) throughout the day, while a dose reduction may be warranted if there are intolerable side effects.

There is no maximum dose for opioids in cancer pain management. The increase or decrease in opioid daily dose is usually approximately 25 - 50% of the total daily dose, taking into consideration patient factors such as organ function, frailty and co-morbidities.[40] However, if the patient persistently requires many rescue doses despite increasing ATC medication, other pain conditions need to be considered and further assistance from specialist is required.

Options of titration:

- Calculate the total daily dose of 4-hourly opioid + dose of opioids taken for breakthrough pain over the last 24 hours (Limit to 50% dose increment within 24 hours. If >50% increment is needed, to consult specialist.)
  OR
- Increase opioid daily dose (25 - 50% of the daily dose) for patient who takes no rescue doses but still has uncontrolled pain

Example 1:

To determine the new dose of opioids, the total daily dose of opioid is calculated (4-hourly opioid added with the total dose of opioids taken for breakthrough pain over the last 24 hours). This is divided by 6 to give the new regular 4-hourly doses.

Patient is on aqueous morphine 5 mg 4-hourly and takes 3 extra rescue doses.
Total 24h morphine = (5 mg x 6) + (5 mg x 3) = 45 mg/24h
New 4-hourly dose: 45 mg/6 = 7.5 mg (rounded down to nearest mg)
Prescription: aqueous morphine 7 mg 4-hourly and 7 mg PRN

Example 2:
Patient is on aqueous morphine 5 mg 4-hourly and takes no rescue doses but still has uncontrolled pain.
Total 24h morphine = (5 mg x 6) = 30 mg/24h
NEW 24h morphine = 30 mg + 25% of 30 mg (7.5 mg) = 37.5 mg
New 4-hourly dose: 37.5 mg/6 = 6.25 mg (rounded down to nearest mg)
Prescription: aqueous morphine 6 mg 4-hourly and 6 mg PRN

- **Maintenance**

Once pain control is adequate and a stable effective dose has been determined, long-acting opioid formulations may be considered for ease of administration.

Long-acting morphine or oxycodone oral formulations are taken every 12 hours, while transdermal fentanyl patches are applied every 72 hours.

Example 3:
Patient's pain control is adequate with aqueous morphine 7.5 mg 4-hourly and no additional doses required for breakthrough pain.
Total 24h morphine = 7.5 mg x 6 = 45 mg
Convert to Tab morphine SR = 45 mg/2 = 22.5 mg
Prescription: Tab morphine SR 20* mg BD (morphine SR available in 10 mg & 30 mg tabs)
*Rounding of the prescription dose is based on drug strength availability.

In patients presenting with severe cancer pain, rapid titration using parenteral opioids may be useful in controlling patient's initial pain. Refer to **Algorithm 2** on **Titration of Morphine for Rapid Pain Relief in Adults with Severe Pain and Distress**.

- **Morphine therapy:**[9]
  - should be titrated according to individual analgesic response and occurrence of AEs
  - should be initiated at the dose of 5 - 10 mg 4-hourly using the oral IR formulation
  - should be started with a lower dose of 2.5 - 5 mg 4 - 6-hourly of the IR formulation in the elderly
- Rapid titration using IV or SC morphine is preferred in patients presenting with severe cancer pain for initial pain control.[9]
- There is no maximum dose for strong opioids in cancer pain management.[9]
- Alternative methods of administration:
  - 4-hourly parenteral morphine/oxycodone
  - continous parenteral opioid infusion
- Long-term use of opioids must not be abruptly discontinued to avoid withdrawal. Tapering opioid therapy must be conducted in a stepwise fashion, involving patients throughout the process.[40]

Recommendation 6
- Patients with persistent cancer pain should be prescribed with regular (around-the-clock) analgesia.
  - Opioid doses must be titrated to achieve optimal pain relief with minimal adverse events.
  - Long-acting opioid formulations may be considered for patients once the effective opioid dose has been established.

4.4.4 Breakthrough pain management

- Breakthrough pain in cancer refers to an exacerbation of pain in the setting of chronic pain managed with analgesics around-the-clock.[11]
- Breakthrough pain:[41]
  - typically, is of rapid onset, severe in intensity and self-limiting, with an average duration of 30 min
  - affects over 50% of patients with cancer
  - may lead to anxiety, depression, decreased functioning and prolonged stays in hospital

Every patient on an opioid should have access to rescue analgesia in order to ensure optimal pain control. There are two subtypes of breakthrough pain which are spontaneous pain and incident pain. Spontaneous pain is sudden and has no identifiable trigger. On the other hand, incident pain is related to an activity e.g. movement and is predictable. Incident pain therefore may be managed by taking medication prior to the action which precipitates it.[41] This needs to be differentiated from end-of-dose failure which occurs when medication wears off before the next regular analgesic dose is due. End-of-dose failure often happens just prior to the next scheduled dose of medication and may be attributed to inadequate analgesic doses or dose intervals exceeding the medication's duration of minimum effective plasma level for pain control.[42]

The consensus and standard of care have been on using 5% to 15% (up to 20%) of the morphine equivalent daily dose (MEDD) in the form of an oral IR opioid to manage transient pain episodes.[43, level III] Evidence to establish the appropriate dose of morphine for breakthrough pain is lacking. However, the widely accepted ratio of the rescue dose to the "around-the-clock" (ATC) medication has been 1/6 i.e. equivalent to the 4-hourly opioid dose. In cases where smaller rescue doses are required e.g. in renal impairment, doses as low as 1/12 of the 24-hour dose can be used. This 'rescue' dose may be given as frequently as required (up to hourly). The ATC dose may be adjusted considering the total amount of rescue morphine taken for the last 24 hours.[9; 44, level I]

A cross-sectional study on patients with advanced cancer reported that the vast majority (89%) of patients with breakthrough pain who had adequately controlled background pain (rated as ≤3 on ESAS pain scale 0 - 10) found oral IR opioid to be either effective or very effective in controlling their breakthrough pain episodes.[43, level III]

IV opioid titration and bolus administration have also been used to improve control of breakthrough pain.[28]

Oral transmucosal fentanyl citrate (OTFC) which is available in Malaysia as sublingual fentanyl is only indicated for breakthrough cancer pain and its method of use is markedly different from other IR opioids. The total OTFC dose taken cannot be used to calculate and titrate the new ATC dose. Careful patient selection, titration and monitoring are required to ensure its optimal use. It is not interchangeable with other IR opioids. It should only be used in adults on regular strong opioids (oral morphine 60 mg/24h) for ≥1 week.[34]

A non-inferiority clinical trial did not demonstrate fentanyl sublingual tablets (FST) 100 mcg being non-inferior to SC morphine 5 mg. Patients taking FST received a second drug dose after 30 min more frequently than those taking SC morphine with a non-significant RD of -13%. Thus, FST cannot be generally recommended as a substitute for SC morphine.[45, level I]

In a non-randomised clinical trial on breakthrough pain, the mean pain intensity levels were significantly lower with FST than oral morphine solution at day 3, 7, 15 and 30. FST also provided significantly faster relief and a shorter dose titration period.[46, level II-1]

- Rescue dose for breakthrough pain is given as often as required (up to hourly).[9]
- ATC dose is adjusted considering the total amount of rescue dose for the last 24 hours.[9]

Recommendation 7
- All patients with cancer pain who are on opioids should be prescribed with rescue analgesia if required to ensure optimal pain control.
- Opioids (morphine or oxycodone) for breakthrough cancer pain should be prescribed at 1/6 to 1/12 of the 24-hour dose.

4.4.5. Opioid rotation

Opioid rotation is a strategy of switching from one opioid to another to improve pain relief or reduce AEs.

This strategy may be indicated in up to 44% of patients with cancer-related pain. Improvement in pain as well as reduced AEs after rotation were seen in 50 - 90% of these patients. Uncontrolled pain was the main reason for opioid rotation in the outpatient setting while AEs were the reason in the inpatient setting where patients were often more debilitated.[47, level III]

- Common indications for opioid switching include:[47, level III]
  - inadequate pain relief despite appropriate titration
  - intolerable AEs (e.g. sedation, nausea, vomiting, constipation)
  - organ impairment
  - practical considerations (e.g. lack of compliance, inability to swallow)

In a large systematic review on opioid rotation, the findings were:[48, level I]

- all studies showed pain improvement or stable pain relief with opioid rotation
- dose titration may still be necessary to achieve stable analgesia
- no particular opioid demonstrated superiority to another opioid
- a higher dosage of the first-line opioid tended to result in lower success rates of rotation
- reduction of AEs was limited with rotation, but patient's satisfaction was generally positive ranging from 60 - 90%

Rotating between opioids remains challenging due to a lack of well-established evidence to support the dose conversions used in clinical practice, and more so in complex cases when there is a need to balance between pain relief and AEs. To address this, a common suggestion is to reduce the calculated dose by 25 - 50% when initiating opioid rotation and titrate upwards accordingly.[9] Because of individual variability, the conversion between opioids should always take into consideration the patient's co-morbidities, concomitant medications, pain and AE intensity and also any pharmacokinetic factors that could influence the effectiveness of the medications.

A systematic review that specifically looked at equianalgesic opioid doses reported the following conversion ratios:[28]

- morphine-oxycodone of 1.5:1
- oral morphine-transdermal fentanyl of 100:1

The conversion ratio from different opioids to methadone was highly variable, ranging from 5:1 to 10:1.

The suggested conversion ratio is shown in **Table 4**.

Table 4. Suggested Dose Conversion Ratio in The Direction Specified

FROM \ TO	Oral morphine mg/day	SC morphine mg/day	Oral oxycodone mg/day	SC oxycodone mg/day	TD fentanyl mcg/h
Oral morphine mg/day		2	1.5	3	3
SC morphine mg/day	2		0.7	1.5	1.5
Oral oxycodone mg/day	1.5	0.7		2	2
SC oxycodone mg/day	3	1.5	2		1
TD fentanyl mcg/h	3	1.5	2	1	

MULTIPLY **DIVIDE**

Adapted: Ministry of Health, Malaysia. CPG Management of Cancer Pain. Putrajaya: MoH; 2010.

Note: Instructions for using the 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. When changing from one opioid to another, consider a dose reduction of 25 - 50% due to incomplete cross-tolerance.
3. Consider reduced doses in the elderly and in patients with renal or significant hepatic impairment.
4. Calculate the total 24-hour opioid dose in mg (for fentanyl, note that the hourly rate is in mcg).
5. Begin at the left-hand column and identify the opioid currently used.
6. Select the alternative opioid from the top row.
7. Identify the box where the column and row intersect and determine the conversion factor to divide or multiply in order to obtain the 24-hour dose of the alternative opioid.
8. Divide 24-hour dose according to the dosing frequency required (for example divide by 2 for BD dosing and divide by 6 for 4-hourly dosing).
9. Calculate the rescue dose for breakthrough pain for each opioid as approximately 1/6 to 1/12 of the total daily dose.
10. **Additional conversions:**
    - PO dihydrocodeine 90 mg/day = PO morphine 10 - 12 mg/day
    - PO tramadol 150 mg/day = PO morphine 15 - 30 mg/day
    - TD fentanyl 25 mcg/hour = continuous SC/IV infusion fentanyl 25 mcg/hour
    - SC morphine = IV morphine

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 CR oxycodone = 30 mg twice daily

Example 2:
Conversion of oral morphine to transdermal fentanyl
Oral morphine mg/day (16 mg 4-hourly = 100 mg per day)
Conversion factor = divide by 3
Equivalent dose of transdermal fentanyl = 100 ÷ 3 = 33 mcg per hour
Reduce equivalent dose by 25% = 25 mcg per hour (due to incomplete cross-tolerance)
Therefore, dose of TD fentanyl = 25 mcg per hour

Recommendation 8
- Opioid rotation should be considered in patients with cancer pain who are not responding to dose escalation or experiencing intolerable adverse events.

4.4.6 Opioids requiring special attention

- **Methadone**

Methadone is an alternative treatment in specialist services for special circumstances e.g. difficult pain, renal impairment, neuropathic pain syndrome and hyperalgesic states. Its use in cancer pain management needs careful consideration and expertise due to its complex pharmacology. In Malaysia, methadone is mainly used for harm reduction in Methadone Replacement Therapy. However, its method of use is different in treating cancer pain.

In a Cochrane systematic review of six studies on the effectiveness and tolerability of methadone as an analgesic for cancer pain vs active comparators, the findings were:[49, level I]
- methadone was similar to morphine in the effectiveness of pain control
- methadone was well tolerated; however, somnolence was more common with methadone while dry mouth was more common with morphine

Based on GRADE, the quality of evidence in this review was low to very low.

In another systematic review of 10 small studies on cancer pain, methadone was effective and safe as a first-line analgesic.[50, level I]

However, no quality assessment of primary studies was mentioned.

WHO guidelines state that due to the complex nature and wide inter-individual variation in its pharmacokinetics, methadone should be initiated only by practitioners experienced in cancer pain.[11]

Recommendation 9
- Methadone may be considered in the management of cancer pain
  - It should only be prescribed by healthcare providers experienced with its use in the management of cancer pain.

- **Pethidine**

Pethidine should not be used in chronic cancer pain management. Long-term pethidine use or at high doses pose a risk of toxic metabolite (norpethidine) accumulation and can cause seizures. Its use may have an increased risk of addiction and is associated with higher incidence of euphoria.[9]

Recommendation 10
- Pethidine should not be used in the management of cancer pain.

4.4.7 Opioids use in special populations

- **Renal and liver impairment**

Renal and liver impairment alter the pharmacokinetics of many medications including opioids by changing opioid metabolism and reducing its clearance, resulting in accumulation of the opioid metabolites. These generally result in more AEs and an increased risk of toxicity. There is limited evidence examining the use of opioids in cancer patients with renal and liver impairment.

The use of opioids in cancer patients with renal impairment is based on pharmacokinetic data, extrapolation of evidence in non-cancer patients and clinical experience. Clinical evidence on the use of opioids in cancer patients with renal impairment was scarce and of very low quality.[39, level I; 51, level I] Given the lack of relevant clinical data, the stratification of risk is guided by the activity of its metabolites and its potential to accumulate.

Morphine is metabolised in the liver to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Both are excreted in the urine. M3G is an inactive metabolite, while M6G is active and both accumulate in renal impairment. Accumulation of M6G is associated with central nervous system AEs and respiratory depression.[9]

A systematic review of 18 studies to evaluate the use of opioids in cancer patients with renal impairment revealed substantial disagreement within the existing literature on the relationship between creatinine clearance and the clearance of morphine and its metabolites.[51, level I] There was an increased chance of toxicity when morphine was used in patients with renal impairment. Patients with renal impairment (<90 ml/min/1.73 m^2) treated with morphine had higher odds of having severe constipation (OR=1.91, 95 % CI 1.08 to 3.37) compared with those with normal renal function. Higher serum morphine concentrations were more likely to lead to severe cognitive dysfunction (OR=1.77, 95 % CI 1.13 to 2.78).[51, level I] The significant predictors of morphine intolerance were age >78 years, high white cell count and high platelet count on concomitant poor liver or renal function.[51, level I]

Elimination of oxycodone and its metabolites was significantly prolonged in renal impairment. Hence, these patients with increased serum concentrations of oxycodone were more likely to report severe fatigue (OR=1.70, 95% CI 1.04 to 2.78).[51, level I]

In another systematic review of 15 studies on the use of opioids for cancer patients with moderate to severe cancer pain and renal impairment, no studies were able to identify the risk of toxicity of opioids in the patients. There was also no direct clinical evidence on the use of any opioids in renal impairment or level of impairment where caution is needed.[39, level I]

Fentanyl is metabolised in the liver and its metabolites have minimal or no pharmacological effect. It is least likely to cause harm when used appropriately.[39, level I]

Recommendations on the use of opioids in cancer-related pain with eGFR of 30 - 89 ml/min (mild to moderate renal impairment) are as follows:[39, level I]

- assess for any reversible factors
- all opioids that are appropriate for cancer pain can be used with consideration of a reduced dose or frequency
- monitor for changes in renal function and consider opioid switching in rapidly deteriorating renal function
- be aware that estimations of GFR may be less accurate in the presence of cachexia, low protein states, oedema and acute renal failure; a lower eGFR should prompt consideration of a change of opioid to one considered safer in renal impairment

There was also lack of good clinical data on opioid treatment in cancer patients with hepatic impairment. In a systematic review of three studies assessing opioid use in cancer patients with hepatic impairment, there was an increase in morphine and M6G concentrations although this

was not significant. Therefore, there was a need for dose adjustment for morphine and oxycodone. The available evidence was heterogeneous and of low quality.[52, level I]

In the earlier edition of MoH CPG on Cancer Pain, it was stated that all opioids should be used cautiously and at reduced doses and/or reduced frequency in patients with renal and/or liver impairment.[9]

- **Older adults**

There is paucity of data on the use of opioids in older adults with cancer pain. Advanced age has greater vulnerability with a proportion of this population having multiple co-morbidities. Challenges in pain assessment, concomitant medical conditions, cognitive impairment e.g. dementia, increasing frailty and loss of physiologic reserve may decrease their capacity to deal with pain and its treatment effectively. Polypharmacy and co-morbid diseases may also reduce the type of available treatment options.[3]

Effective and safe cancer pain management in older adults requires careful assessment and individualised care.

- In older adults with cancer pain, the general principle of treatment is to start medication at a low dose and titrate slowly.

Recommendation 11
- In the management of cancer pain for older patients or those with renal/liver impairment:
  - All opioids should be used with caution.*
  - Adjustment in doses/frequency of opioids should be considered.

*Fentanyl is a safer opioid in renal impairment.

4.4.8 Opioid side effects

Opioids are generally well-tolerated and safe in cancer pain management.[9] In a large systematic review of 25 studies, nausea and constipation were most common, whilst vomiting, drowsiness and dry mouth were less frequent.[54, level I]

There was a dose-effect relationship, where higher rates of AEs were seen with higher opioid starting doses and higher doses after titration, particularly in morphine.[54, level I] Awareness of these AEs is vital to ensure compliance and optimal pain control.

Management strategies include awareness and recognition of the AEs, symptomatic management of individual AEs and adjustment of opioid dosages, including dose reduction and opioid switching. Refer to **Appendix 5a** for **Suggested Medication Dosages and Adverse Events in Adults.** The management of the side effects is discussed below.

- Constipation
  - Constipation is the commonest reported AE with a 25% incidence rate.[53, level I]
  - Concurrent prophylaxis for constipation e.g. stimulants and softening laxatives is recommended for all patients on regular opioid therapy.[9]
  - The rate of constipation is lower for fentanyl than morphine.[54, level I] Thus, fentanyl can be considered as an alternative in severe morphine-induced constipation.[9]
- Nausea and vomiting
  - Nausea occurs in 21% while vomiting in 13% of patients on opioid therapy.[53, level I]
  - These AEs are temporary and tolerance commonly develops in 5 -10 days after initiation of opioids.[9]
  - Anti-emetics e.g. metoclopramide, haloperidol and prochlorperazine can be used to treat these AEs.[9]
- Dry mouth
  - The incidences of dry mouth are variable, ranging from 17%[53, level I] to 94%.[54, level I]
  - It is particularly important, as patients on opioid therapy rated the symptom as moderate to severe.[54, level I] Non-pharmacological measures e.g. oral hygiene, sugar-free chewing gum/candies, and saliva stimulant mouth spray/gel can be offered to patients to improve their symptoms.
- Sedation and drowsiness
  - Sedation can occur at the initiation of opioid therapy and tends to resolve within a week.[9]
  - Somnolence is reported in 13% of patients[53, level I] and drowsiness in up to 88%, with the rate of drowsiness higher in oxycodone compared with other opioids, even where low doses are used.[54, level I]
  - In many patients, symptoms are brief and patient education is sufficient. For patients with co-morbidities (metabolic encephalopathy, dementia) and on concomitant sedation use, prolonged sedation may occur.[9]
  - Management strategies include dose reduction, titration using the lowest effective dose, and opioid switching.[9] Methylphenidate and other psychostimulant drugs can be considered if necessary.[9; 40]
- Delirium and neurotoxicity (including confusion and myoclonus)
  - Transient mild cognitive impairment may occur upon opioid initiation and usually resolves within 1 - 2 weeks.[9]

- Persistent delirium should prompt further investigation for its causes (e.g. hypercalcaemia, sepsis and electrolytes imbalances) whenever appropriate.
- A dose reduction of 25% with opioid switching may resolve delirium. Low-dose antipsychotics e.g. haloperidol may be used.[9]
- Opioid-induced myoclonus is usually mild and can be managed by dose reduction and opioid switching. In a systematic review of 25 studies on opioid-related AEs, there was no report on myoclonus.[54, level I] Pharmacological management using clonazepam, sodium valproate and baclofen can be considered.[9]

• Pruritus
- Puritus can occasionally occur as an AE and has been reported up to 9%.[54, level I] It is more common after neuroaxial opioid delivery.
- Antihistamines can be considered and opioid switching may be necessary if the symptom is severe.

• Other AEs
- Opioid-induced endocrinopathy
  Cancer patients are surviving longer with the advancement of oncological management.
  - Long-term opioid treatment in surviving patients with cancer-related pain has been shown to affect the endocrine system.[55, level III]
  - Patient education, close follow-up, use of the lowest effective opioid dose and opioid tapering may be considered in this patient population.[40]
- Opioid-induced hyperalgesia[56]
  - It is a state of nociceptive sensitisation caused by exposure to opioids.
  - It is characterised by a paradoxical response whereby a patient receiving opioids for the treatment of pain could become more sensitive to certain painful stimuli.
  - Refer to pain or palliative care physicians for further management.

The management of opioid side effects is shown in Table 5 below. Refer to **Appendix 5a** for **Suggested Medication Dosages and Adverse Effects in Adults.**

Table 5. Management of Opioid Side Effects

Side Effects	Management
Constipation	Faecal softeners • lactulose • macrogol Stimulant laxatives • bisacodyl • senna
Nausea and Vomiting	Anti-emetics • Metoclopramide • Haloperidol • Prochlorperazine
Dry Mouth	Non-pharmacological treatment: • Good oral hygiene • Sugar-free chewing gum and candies/sweets • Saliva stimulants (e.g. mouth spray/gel)
Sedation and drowsiness	• Opioid dose reduction, titrate to the lowest effective dose, and consider opioid switching • Methylphenidate and other psychostimulant drugs can be considered if necessary
Delirium and neurotoxicity (e.g. confusion and myoclonus)	• Can be managed by dose reduction and opioid switching • Can consider using clonazepam, sodium valproate and baclofen for myoclonus • Can consider antipsychotics for delirium
Pruritus	• May consider antihistamines • Opioid switching may be necessary if the symptoms are severe

4.4.9. Opioid toxicity

- **Respiratory depression**

Respiratory depression is a result of opioid toxicity. It is a very rare event that may occur during rapid titration.[9] It is uncommon during chronic administration.[40] When appropriately titrated against the patient's pain, strong opioids do not cause clinically important respiratory depression.[34]

Sedation almost always precedes respiratory depression. Therefore, sedation assessment is a good early clinical indicator of opioid-induced respiratory depression.[9]

If severe respiratory depression occurs (respiratory rate <8/minute), very low doses of naloxone at 40 mcg (0.04 mg) can be used and titrated every 1 - 3 minutes against the patient's respiratory rate. Large bolus doses of naloxone should not be given as it reverses the analgesic effects and causes major physical withdrawal syndromes. Severe hypertension, pulmonary oedema, cardiac arrhythmia and cardiac arrest have been reported with naloxone use.[34]

Refer to **Appendix 7** for **Guide for Naloxone Use**.

Recommendation 12
- Opioid-induced side effects should be proactively identified and treated adequately to ensure optimum cancer pain management.
- Laxatives should be prophylactically prescribed in patients with cancer pain and on regular opioid therapy.

4.4.10 Tolerance and addiction to opioids

- **Tolerance to opioids**

Opioid tolerance is defined as a long-term body adaptation to opioids resulting in reduced clinical effectiveness of opioids with repeated use at the same dose.[57]

Opioid tolerance in cancer is known to be contributed by the downregulation of mu-receptors in neuronal cells. The exact mechanism is still not well understood. Persistent pain, chronic opioid administration and reduced expression of opioid receptors on certain types of cancer cells are possible causes of mu-receptor downregulation.[58]

Fear of opioid tolerance should not cause any hesitation to start or increase opioid therapy for cancer patients experiencing pain. 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 a pain specialist or palliative medicine specialist.[9]

- **Addiction/misuse of opioids**

The incidence of opioid misuse in advanced cancer patients differs widely between studies in a recent systematic review. Particularly among children, adolescents and young adults, misuse behaviours were reported to range from 7% to 90%.[59, level I] Nonspecific substance use disorders were reported to range between 2% to 35% of adults with cancer. It is unclear if this included treatment-related opioid dependence or misuse.[60, level I]

Multiple risk factors for opioid misuse or abuse have been identified among patients with cancer e.g:[61]
- history of dependence or misuse of prescription drugs, illicit drugs or alcohol prior to cancer diagnosis/treatment
- history of binge drinking (alcohol) or peers who binge drink
- family history of substance abuse
- history of psychiatric disorder including anxiety, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder, bipolar disorder or schizophrenia

- history of sexual abuse victimisation
- young age (<45 years old)
- history of legal problems or incarceration

Tools for recognising and predicting opioid misuse are available for clinical use. The NCCN guidelines suggest the use of Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) and the Opioid Risk Tool (ORT) for patients considered for long-term opioid therapy in predicting opioid misuse. For patients already on opioids, the guidelines suggest the Current Opioid Misuse Measure (COMM) tool to detect aberrant behaviour associated with opioid misuse.[61]

- It is important to identify patients at risk of opioid misuse so that they can be closely monitored.
- Fear of opioid misuse or tolerance should not preclude the start of opioid therapy for cancer patients experiencing pain.

4.5 Adjuvants

Adjuvant analgesics are medications with primary indications other than pain. However, they are useful in managing certain painful conditions, particularly neuropathic pain. The most common classes of adjuvant analgesics used in cancer pain management are anticonvulsants, antidepressants and corticosteroids. Evidence for the use of these medications was largely extrapolated from studies on non-cancer pain.

- **Anticonvulsants**

A large meta-analysis on patients with neuropathic pain including cancer-related neuropathic pain reported the following NNT to achieve 50% pain relief and NNH for the following anticonvulsants:[62, level I]

- gabapentin (900 - 3600 mg/day): NNT 6.3 (95% CI 5.0 to 8.3) and NNH 25.6 (95% CI 15.3 to 78.6)
- pregabalin (150 - 600 mg/day): NNT 7.7 (95 % CI 6.5 to 9.4) and NNH 13.9 (95% CI 11.6 to 17.4)

There was no evidence on a dose-response effect for gabapentin, while pregabalin showed a better response at higher doses. Combination therapy of gabapentin with morphine was superior to monotherapy. Studies using other antiepileptic agents were mostly negative. The recommendation on the anticonvulsants based on GRADE was strong.

In a Cochrane systematic review, a small RCT on cancer-related neuropathic pain showed that gabapentin 1800 mg daily and pregabalin 600 mg decreased pain scores, had a morphine-sparing effect and improved functional capacity. The quality of the evidence was very low.[63, level I]

However, a meta-analysis on patients with tumour-related cancer pain demonstrated that adding gabapentin or pregabalin to stable opioid analgesia did not improve pain intensity. The quality of evidence was low.[64, level I]

The Cochrane systematic review above reported that 63% of those on gabapentin (1200 mg/day or more) experienced at least one AE, compared with 49% on placebo (RR=1.3, 95% CI 1.2 to 1.4; NNH=7.5 95% CI 6.1 to 9.6). The most common AEs reported were somnolence and dizziness, peripheral oedema and ataxia/gait disturbances.[63, level I]

- **Antidepressants**

A meta-analysis on patients with neuropathic pain including cancer-related neuropathic pain gave an NNT to achieve 50% pain relief of 3.6 (95% CI 3.0 to 4.4) for amitriptyline and 6.4 (95% CI 5.2 to 8.4) for selective norepinephrine reuptake inhibitors (SNRIs) e.g. duloxetine and venlafaxine. The NNH were 13.4 (95% CI 9.3 to 24.4) for amitriptyline and 11.8 (95% CI 9.5 to 15.2) for the SNRIs. There was no evidence of a dose-response effect for amitriptyline. The final quality of evidence was moderate for amitriptyline and high for SNRIs.[62, level I]

In a Cochrane systematic review, two clinical trials assessed the effectiveness of amitriptyline in cancer-related neuropathic pain. Only one trial showed that amitriptyline 50 - 100 mg decreased mean pain intensity, had a morphine-sparing effect and improved functional capacity. The quality of the evidence was very low.[65, level I]

In another systematic review, an RCT on patients with chemotherapy-induced peripheral neuropathy, showed that duloxetine was more effective than placebo in pain relief (MD=0.73, 95% 0.26 to 1.20). The quality of the evidence was low based on GRADE.[4, level I]

Another RCT in a systematic review on patients with tumour-related cancer pain demonstrated that adding amitriptyline to stable opioid analgesia did not improve pain relief. The quality of evidence was low.[64, level I]

A Cochrane systematic review reported that 55% of patients on amitriptyline experienced at least one AE compared with 36% in those on placebo (RR=1.5, 95% CI 1.3 to 1.8; NNH=5.2, 95% CI 3.6 to 9.1). The most commonly reported AEs were somnolence, dizziness, dryness of mouth, nausea and constipation.[64, level I]

The previous local CPG on cancer pain recommends that neuropathic cancer pain may be treated with antidepressants and/or anticonvulsants.[9] Despite the lack of high-quality evidence, WHO guidelines also suggests

that practitioners may consider anticonvulsants and/or antidepressants for patients with inadequate pain relief or intolerable AEs to opioids.[11]

- **Corticosteroids**

Due to their anti-inflammatory mechanism of action, corticosteroids are used as adjuvant analgesics for pain associated with inflammation e.g. headache from brain metastases, abdominal pain from liver capsule distension or intestinal obstruction and neuropathic pain from spinal cord compression.[9] A Cochrane systematic review found that corticosteroids were more effective than controls in cancer pain for up to one week of intervention (MD= -0.84, 95% CI -1.38 to -0.30). The most common AEs attributed to the medication were restlessness, insomnia, GI and cardiovascular (CV) events, Cushingoid facies, anxiety, fluid retention, hypocalcaemia and hyperglycaemia. An improvement in quality of life or patient well-being had also been reported.[66, level I] However, current evidence from this systematic review is insufficient to establish an ideal dose, duration of therapy and route of administration of corticosteroids for the relief of cancer pain. Therefore, it is advocated that clinicians prescribe corticosteroids cautiously for cancer pain management i.e. carefully assess the benefit, treat for the shortest duration and discontinue early if ineffective.

- **Bone targeting agents**

Bisphosphonates inhibit osteoclast activity and are used as supportive treatment to prevent or delay the occurrence of skeletal-related events (SRE) (i.e. pathological fractures, spinal cord compression, surgery and radiotherapy to the bone, and hypercalcemia) in patients with bone metastases. They have been found to reduce pain and analgesic requirements in certain cases. However, the mechanism of its pain-relieving effect is poorly understood. Examples include clodronate, ibandronate, pamidronate, risendronate, etidronate and zoledronate. Denosumab is a monoclonal antibody that is directed against the receptor activator of the nuclear factor kappa beta (RANK) ligand which leads to a decrease in osteoclastogenesis and osteoclast activity, hence reducing bone resorption.[9; 11]

Three recent systematic reviews assessed the effectiveness of different bone targeting agents in patients of various cancers [i.e. breast, prostate and non-small cell lung cancer (NSCLC)] with bone metastases. The first systematic review on bisphosphonates and denosumab on pain relief and QoL reported that there was no high-level evidence that any of these agents reduced or prevented pain or improved QoL in NSCLC patients.[67, level I]

On the other hand, a Cochrane review assessing the effects of bisphosphonates and other bone agents in addition to anticancer treatment found that in women with metastatic breast cancer and bone

metastases, bisphosphonates appeared to reduce bone pain compared with placebo in six out of 11 studies. The quality of the evidence based on GRADE was moderate.[68, level I]

Meanwhile, a Cochrane network meta-analysis of patients with prostate cancer and bone metastases receiving bisphosphonates or RANK-ligand-inhibitors reported the following findings.[69, level I]

- For the outcome of the proportion of patients with pain response, zoledronate was ranked as the best treatment option followed by etidronate, clodronate, and risedronate. However, only zoledronate was found to be more effective than clodronate in pair-wise comparison (RR=1.19, 95% CI 1.03 to 1.39). There was no trial reported on denosumab in pair-wise comparison.
- For the outcome of renal impairment, compared with no treatment/placebo, zoledronate increased the risk (RR=1.63, 95% CI 1.08 to 2.45) while clodronate did not show any significant risk. By comparing the different bone targeting agents with each other, no significant differences were shown.
- For the outcome of osteonecrosis of the jaw (ONJ), compared with no treatment/placebo, denosumab increased the occurrence of ONJ (RR=3.45, 95% CI 1.06 to 11.24) while zoledronate and clodronate did not show significant difference in the outcome. By comparing the different bone targeting agents with each other, no significant differences were found.
- For the outcome of Grade 3 to 4 AEs (fatigue, diarrhoea and nausea), compared with no treatment/placebo, only denosumab increased the risk of the AEs (RR=1.46, 95% CI 1.06 to 1.99). By comparing the different bone targeting agents with each other, zoledronate had a lower risk of AEs compared with denosumab (RR=0.92, 95% CI 0.87 to 0.98). The comparison between the other agents were not significant.

WHO guidelines on cancer pain management:[11]

- recommends that bisphosphonate should be used to prevent and treat bone pain in adults (including older persons) and adolescents with bone metastases
- has no recommendation for or against the use of monoclonal antibodies to prevent and treat bone pain
- also has no recommendation for or against the comparative advantage of monoclonal antibodies over bisphosphonates to prevent and treat bone pain

- **Others**

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, a Cochrane systematic review showed insufficient evidence to make any conclusion

on the clinical benefit of ketamine as an adjuvant to opioids for the relief of cancer pain. Hallucinations and cognitive disturbance were reported at higher doses of ketamine. One RCT included in the review demonstrated twice the incidence of AEs when a rapid dose escalation method was employed.[70, level I]

In the previous guidelines, ketamine was recommended to be considered in patients with poorly controlled cancer pain despite optimal opioid therapy. It may be used by specialists familiar with cancer pain management or palliative medicine/pain specialists.[9]

- Ketamine is sometimes used as an adjunct to opioids in patients with cancer pain.

Recommendation 13
- Anticonvulsants or antidepressants may be considered in patients with neuropathic cancer pain.
- Corticosteroids may be used cautiously as an adjuvant in patients with specific cancer pain syndromes.
- Bone targeting agents may be used in cancer patients with painful bone metastasis.

4.6 Medical Cannabis

Medical cannabis is a term used to describe cannabis used for medical purposes. In recent years, there has been increasing interest in the potential therapeutic use of cannabis for various medical conditions including chronic pain. However, there is still much debate surrounding the issue due to concerns about its safety and effectiveness.

Evidence mapping of systematic reviews on the therapeutic effects of medicinal cannabis reported that the evidence was broad, highly heterogeneous in methodology and with conflicting conclusions. In fact, there was a limited number of studies that investigated cancer pain relief by medicinal cannabis.[71, level I]

A meta-analysis that included five RCTs showed that adding medical cannabis to opioid therapy:[72, level I]
- resulted in a non-significant trivial reduction in cancer pain (WMD= -0.18 cm on the 10 cm Visual Analogue Scale (VAS) for pain, 95% CI -0.38 to 0.02) based on high certainty evidence
- increased incidence of nausea (RR=1.43, 95% CI 1.04 to 1.96) and vomiting (RR=1.50, 95% CI 1.01 to 2.24) based on moderate certainty evidence

The above meta-analysis was supported by another meta-analysis of four RCTs comparing medical cannabis and placebo. There was a non-significant pain reduction (WMD= -0.1, 95% CI -0.28 to 0.09) with a significantly higher risk of transient cognitive impairment, vomiting, drowsiness, impaired attention and nausea in those taking medical cannabis.[73, level I]

A Malaysian health technology assessment reported that current evidence was inadequate to recommend the use of medical cannabis in cancer pain.[74]

A 2023 meta-analysis on RCTs showed that medical cannabinoids had no significant difference with placebo in pain reduction or occurrence of serious AEs. However, the quality of the evidence was graded as low based on GRADE.[75, level I]

- There is insufficient evidence to formulate a recommendation for medical cannabis use in cancer pain.

4.7 Anticancer Therapy

Radiotherapy, chemotherapy and hormonal therapy are important components of anticancer therapy. These therapies especially radiotherapy may be a strategy for multidisciplinary management of cancer pain.

- **Radiotherapy**

Radiotherapy has been used to reduce pain and requirements of analgesics in symptomatic bone metastasis. External beam radiotherapy (EBRT) is a type of radiation that could be given to a single or limited number of sites in a patient.

The usual dose-fractionation of radiotherapy schedules for palliation are:

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

Single-fraction EBRT has been shown to be as effective as the fractionated regime in providing pain relief from bone metastases. Two meta-analyses showed no significant difference in complete and overall response rates for pain control between single and multiple fractions of radiotherapy in painful uncomplicated bone metastases. However, the two reviews demonstrated that re-treatment was significantly higher in single fraction with OR ranging from 2.42 to 2.60. In terms of safety, there was no significant difference in toxicities between the two

arms.[76 - 77, level I] Both meta-analyses failed to mention the quality assessment of the primary papers.

Advanced radiotherapy techniques e.g. stereotactic body radiotherapy (SBRT) have also been used in cancer pain. A systematic review of four high-quality RCTs showed:[78, level I]

- SBRT was more effective than conventional RT on pain response rate at three months (RR=1.41, 95% CI 1.12 to 1.77); however, there was no difference at one and six months
- no significant difference in safety outcomes between the groups

Recommendation 14

- Radiotherapy may be offered to control pain in symptomatic bone metastasis.
  - Single-fraction external beam therapy is the preferred choice.

Pain flare-effect (PFE) post-radiotherapy is a phenomenon related to a transient increase in pain. A systematic review of six studies showed that corticosteroids were more effective in reducing PFE compared with placebo in cancer pain (RR=0.67, 95% CI 0.48 to 0.93).[79, level I]

Hemibody radiotherapy for cancer pain in widespread bone metastasis has been mentioned in the previous MoH CPG whereby:[9]

- average time for any pain relief was three days with an average of eight days for maximum relief
- incidence of haematological grade 3 - 4 toxicity is low

Radiotherapy is also used for the reduction of pain related to advanced malignancy which includes:[9]

- thoracic pain from lung cancer
- abdominal and pelvic pain from gynaecological, GI and urological cancers
- pain due to locally advanced head and neck cancers

The pain response rates range from 67% to 77% and overall symptomatic response rates range from 74% to 79%. The commonly used fractionation is palliative hypofractionation.

The CPG also mentions that there is no data on the optimal timing for palliative radiotherapy in painful bone metastasis and pain related to advanced malignancy. However, radiotherapy should be considered early in the course of the disease.[9]

- **Other anticancer therapy**

Other cancer therapies which include chemotherapy and hormonal therapy can be a mode used to reduce pain and improve quality of

life in patients with chemo-sensitive or hormone-sensitive cancers e.g. breast cancer, lung cancer, prostate cancer, lymphoma, ovarian cancer and germ cell tumour.[9]

The treatment landscape of anti cancer therapy has changed with the emergence of immunotherapy. However, the role of immunotherapy in the management of cancer pain is still limited.

In a retrospective cohort study with a propensity score-matched (PSM) analysis comparing four types of anticancer therapy (immunotherapy, chemotherapy, radiotherapy and targeted therapy) in cancer pain, the findings were:[80, level II-2]

- the total oral morphine equivalent daily dose (OMED)(mg) q/day and NRS scores decreased significantly in patients receiving immunotherapy
- compared with the other three treatment groups, the OMED (mg) q/day and NRS were significantly lower in the immunotherapy group after treatment
- fewer AEs were shown in the immunotherapy group compared with the other three groups

- **Radionuclide therapy**

The use of radionuclide therapy for metastatic bone pain, especially in diffuse disease or refractory bone pain is an option.

A systematic review on pain response (partial and complete response) of different bone-seeking radiopharmaceuticals (153Sm,186Re,188Re and 223Ra) for palliation of malignant bone pain from prostate cancer showed:[81, level I]

- pain response of greater than 50 - 60% with each radionuclide
- low incidence of grade 3 and 4 haematological toxicity

There was limited data on the use of radionuclide seeds in metastatic bone pain.[82, level II-1] In view of high cost, limited data and availability, radionuclide and radiation seeds therapy are not a routine option for cancer-related bone pain in this country. Thus, no recommendation can be formulated on its use.

5. PSYCHOSOCIAL INTERVENTION

Pyschoeducation, psychological and spiritual interventions are important in the management of cancer pain. Patients with cancer pain may perceive the pain as the most feared physical consequence. The consequences may be related to losing hope for cure or as a punishment for previous wrongdoings. It can also affect mood and cause anxiety and other psychological symptoms.[9]

5.1 Psychoeducation Intervention

A systematic review of four RCTs reported that educational interventions given by healthcare providers (e.g. provision of educational information, behavioural instructions and advice) showed mixed results in the improvement of pain intensity and interference. Jadad Score of the included studies ranged from 2 - 4.[83, level I]

In a meta-analysis of 12 RCTs, pain education (through interviews ± phone calls) led to a small reduction in pain intensity of cancer patients (SMD= -0.11, 95 % CI -0.20 to -0.02) compared with control. The quality of the primary studies was mixed based on Jadad Score.[84, level I]

5.2 Psychological Intervention

Types of psychological strategies that are available include imagery, relaxation and cognitive restructuring.

A large meta-analysis on psychosocial interventions (psychotherapy, hypnosis, desensitisation or meditation) in patients with cancer showed moderate positive effects on pain severity (Hedge's g=0.34, 95% CI 0.23 to 0.46) and pain interference (Hedge's g=0.40, 95% CI 0.21 to 0.60) compared with control. One of the limitations of this meta-analysis was the heterogeneity of primary papers.[85, level I]

An RCT on brief cognitive behavioural strategies intervention in advanced cancer showed lower symptom cluster distress (pain, fatigue and sleep disturbance) only at six weeks of intervention (p=0.04).[86, level I]

Another RCT on patients with alexithymia and cancer pain showed that psychological interventions (psychoeducation, problem-solving, cognitive restructuring of dysfunctional illness-related concerns and beliefs, stress management and progressive relaxation) improved alexithymia in patients with cancer pain which led to a significantly bigger change in score for pain intensity compared with control that received treatment as usual.[87, level I]

Although the evidence for psychoeducation and psychological interventions on cancer pain was of moderate level, their important role in the management of cancer pain should be acknowledged and considered for patients. These interventions usually need sufficient time before benefits are seen.

5.3 Spiritual Intervention

Spiritual intervention is a part of holistic care in alleviating cancer pain which complements physical, psychological and social strategies.

A systematic review of 11 studies that investigated the effectiveness of spiritual intervention (Dignity Therapy, focused narrative intervention and mindfulness-based stress reduction) found paucity and heterogeneity of evidence on cancer pain. Some of the evidence suggested spiritual care may aid in coping with pain rather than altering pain intensity. However, spiritual interventions were well received by the patients and do not appear to cause harm.[88, level I]

Recommendation 15
- Psychoeducation, psychological and spiritual interventions should be considered in the management of cancer pain.

6. INTERVENTIONAL TECHNIQUES/SURGERY

6.1 Neurolysis

Neurolysis which is performed by specialists trained in interventional pain management, requires instilling a chemical ablative solution (e.g. alcohol or phenol with local anaesthetics) or physical ablation (e.g. surgical resection and radiofrequency denervation) into the nerve plexus resulting in nerve destruction or degeneration. Commonly, neurolysis involves ablation of sympathetic ganglia e.g. coeliac plexus or ganglia, splanchnic plexus, superior hypogastric plexus (SHG) and Walther's ganglia or ganglion impar.

A Cochrane systematic review of six RCTs on advanced pancreatic cancer pain in adults showed that coeliac plexus neurolysis (CPN) was more effective for reducing pain than standard analgesic therapy at 4- and 8-weeks follow-up [MD= -0.42 (95% CI -0.70 to -0.13) and MD= -0.44 (95% CI -0.89 to -0.01) respectively]. The risk of bias based on only three domains showed moderate quality of primary papers.[89, level I]

In a recent meta-analysis of 10 RCTs on unresectable pancreatic cancer, pain control was achieved four weeks after CPN using percutaneous, intraoperative or endoscopic approaches compared with standard medical management alone (MD= -0.58, 95% CI -1.09 to -0.07). The main AEs were transient hypotension (20 - 41.7%), inebriation (6.9 - 12.5%), diarrhoea (0 - 25%), burning pain at the injection site (6.9 - 10%) and nausea (8.3%). The quality of the evidence based on GRADE was moderate.[90, level I]

Another meta-analysis on endoscopic ultrasound-guided CPN for pancreatic cancer pain reported a response rate of 46% (95% CI 36 to 55) using a central injection technique. Major adverse complications were spinal stroke which rarely occurred at 0.2% and even more scarce was visceral ischaemia.[91, level I]

Studies for neurolysis of SHG and ganglion impar were limited. A 10-year retrospective cohort study on the effectiveness of SHG for pelvic cancer pain showed a significant pain score reduction in 59.4%, 55.5% and 48.8% of patients at 1-, 3- and 6-months follow-up. The most common AEs were transient hypotension (5.56%) and less common ones were transient urinary incontinence (0.56%), iliac artery puncture (0.56%) and hypertension (0.56%). Repeat injections were done in 5.5% of patients at three months to one-year follow-up.[92, level II-2]

An RCT reported better analgesic response when SHG neurolysis was combined with pulsed radiofrequency of sacral roots up to three months post-injection compared with SHG neurolysis alone in perineal

and pelvic cancer pain (MD= -0.67, 95% CI -1.29 to -0.05). However, AEs were not discussed.[93, level I]

In a pre- and post-study on patients with uncontrolled pelvic oncologic pain with the established therapy or experimenting opioid AEs, ganglion impar neurolysis showed a significant reduction in pain score and morphine consumption up to three months follow-up. AEs were not discussed.[94, level II-3]

Evidence on somatic plexus neurolysis (e.g. brachial or lumbosacral plexus) was confined to case reports.

6.2 Neuraxial Opioids

Neuraxial opioids involve the delivery of drugs via epidural, intrathecal or intracerebroventricular routes. A catheter drug delivery system with the aid of either a subcutaneous implanted device or spinal port with an external syringe pump, provides an effective therapeutic option for refractory cancer pain.

In a cohort of refractory pancreatic cancer pain, 64.3% of patients with intrathecal drug delivery systems experienced >50% pain reduction from baseline after three months of treatment initiation ($p<0.01$).[95, level II-2]

A systematic review for the European Palliative Care Research Collaborative (EPCRC) guidelines found no difference in pain scores between neuraxial bolus and continuous opioid infusion. There was also no difference between epidural morphine and systemic morphine. It was concluded that spinal opioid therapy may be effective for treating cancer pain not adequately controlled by systemic treatment based on weak evidence.[96, level I]

A more recent meta-analysis showed a significant mean pain score reduction of 3.64 (95% 3.09 to 4.18), up to one-month post-implantation based on retrospective studies. Improvements in symptom severity were associated with improved QoL. In addition, all included studies that assessed the use of systemic opioids at baseline showed a dose reduction following implantation. The most common intrathecal opioid was morphine, which was used alone or in combination with adjuvants such as bupivacaine, ropivacaine, clonidine or baclofen.[137, level I]

A prospective product surveillance registry reported severe AEs (SAEs) from intrathecal implantable device comprised of infection (3.2%), post-dural puncture headaches/cerebrospinal fluid leaks (1.27%), pump pocket haematoma (0.28%) and pneumonia (0.14%). Other AEs of systemic opioids may occur in neuraxial opioid therapy e.g. nausea,

pruritus, urinary retention, constipation, respiratory depression, sedation and confusion.[97, level II-2]

6.3 Vertebroplasty

Vertebroplasty is a percutaneous vertebral augmentation procedure that requires an injection of cement into cancellous bone of the vertebral body to relieve pain due to spinal compression fractures caused by osteoporosis or malignant infiltration. The procedure is minimally invasive and relatively safe. It increases stability of the spine by preventing vertebral body collapse. Patients who do not respond to conservative therapy or are poor candidates for open surgery may benefit from vertebroplasty.

A systematic review of seven RCTs with low risk of bias concluded that percutaneous cement vertebroplasty or balloon kyphoplasty, either alone or in combination with other local therapies e.g. iodine-125 seeds, chemotherapy, radiofrequency ablation or corticosteroids, were significantly effective for cancer pain due to malignant spinal compression fractures. The most common procedure-related AEs was cement leakage which occurred at a rate of 24% (95% CI 11 to 44). Nevertheless, there was no significant morbidity or mortality reported.[98, level I]

6.4 Surgical intervention

Surgery has a role in the management of cancer pain. Ablative surgery for large painful tumours e.g. fungating breast lesions or sarcomas may improve pain control where analgesics and other interventions provide suboptimal relief. Palliative surgical operations e.g. colostomy and bypass operations may also relieve pain due to malignant bowel obstruction. The decision for surgical intervention should be made by a multidisciplinary team taking into consideration of other treatment options, risks to the patient and, expectations of patient and family members.[9]

A systematic review found that cordotomy might be effective and safe in mesothelioma-related pain. However, the available evidence was limited in quantity and quality which warranted more reliable evidence to aid decision-making on continued provision of this intervention.[99, level I]

A multicentre cohort study had shown that orthopaedic oncology surgery on metastatic long bone disease significantly improved patients' functional outcome and pain as early as two weeks post-operatively and should be considered for impending or pathologic fracture in patients with expected short-term survival. However, this study also found that

the QoL of the patients did not improve. The overall complication rate was 35% with deep vein thrombosis being the most common.[100, level II-2]

Recommendation 16

- Patients whose pain control is poor despite optimal pharmacological therapy should be referred to specialists trained in interventional pain management for consideration of the following interventions:
  - coeliac plexus neurolysis for advanced pancreatic cancer pain
  - superior hypogastric plexus or ganglion impar neurolysis for advanced pelvic and perineal cancer pain
  - intrathecal drug delivery system
  - vertebroplasty for malignant spinal compression fractures

7. OTHER INTERVENTION

Physical and complementary therapies have gained widespread recognition as valuable interventions for relieving cancer-related symptoms. Numerous studies and clinical trials have investigated the effectiveness and safety of these therapies in improving the well-being and QoL of individuals living with cancer. From exercise programmes to massage therapy, acupuncture and Transcutaneous Electrical Nerve Stimulation (TENS), these approaches offer a diverse range of options to address the unique needs of patients.

A systematic review on the effect of complementary and alternative medicine (CAM) interventions on breast cancer-related pain suggested that CAM should be used cautiously along with other medical treatments to ease cancer-related pain.[101, level I]

- **Transcutaneous Electrical Nerve Stimulation**

A Cochrane systematic review on TENS showed insufficient evidence on its effectiveness in adults with cancer-related pain compared with control (sham/placebo). However, TENS was well tolerated.[102, level I]

- **Exercise**

Exercise, with its potential to alleviate pain, improve physical function and enhance overall well-being, is a promising non-pharmacological intervention for the management of cancer pain.

A systematic review showed that exercise reduced cancer pain compared with non-exercise/usual care although the effect size was small (SMD= -0.45, 95% CI -0.62 to -0.28). Majority of the primary papers were of high risk or with some concern of bias.[103, level I]

- **Massage and aromatherapy**

There is a lack of clear evidence on the effectiveness of massage on pain relief in people with cancer.

A systematic review showed mixed results that massage was effective in reducing cancer pain in patients with advanced cancer.[104, level I]

However, a later meta-analysis of massage therapy on cancer pain found that:[105, level I]

- massage reduced pain compared with no-massage (SMD= -1.25, 95% CI -1.63 to -0.87)
- subgroup analysis showed that body massage, aroma massage and foot reflexology were effective in pain reduction

These are supported by a Cochrane systematic review where massage with or without aromatherapy in people with cancer led to significant medium- and long-term pain relief compared with no massage.[106, level I]

The quality of primary papers in the three-evidence mentioned above were of mixed quality.

Another meta-analysis showed no difference in reduction of cancer pain between aromatherapy massage and control.[107, level I] This is supported by another systematic review on the effect of CAM where massage therapy was found to reduce breast cancer-related pain but aromatherapy alone or in combination with massage did not.[101, level I]

- **Acupuncture**

A Cochrane systematic review showed insufficient evidence on the effectiveness of acupuncture in relieving cancer pain in adults compared with sham acupuncture or analgesics. The findings were:[108, level I]

- acupuncture was effective in managing pancreatic cancer pain, late-stage unspecified cancer pain and chronic neuropathic pain related to cancer
- acupuncture was not effective in ovarian cancer and stomach carcinoma

Specifically on breast cancer, a systematic review found that acupuncture reduced aromatase inhibitor-related pain, post-operative pain and chronic cancer-related pain. The 10 RCTs included were of mixed quality.[101, level I]

A recent systematic review showed that acupuncture used for cancer pain had:[109, level I]

- favourable effect on pain relief in palliative care
- appeared to be a safe treatment for pain management

However, there was no quality assessment reported.

Another systematic review of 14 systematic reviews concluded that clinicians may consider acupuncture as an adjunctive therapy for cancer-related pain management, in particular when pain control was unsatisfactory using analgesics alone. It found that:[110, level I]

- acupuncture and related therapies were more effective at reducing pain than sham acupuncture or no intervention (SMD= -0.30, 95% CI -0.56 to -0.03)
- acupuncture and related therapies alone did not have superior pain-relieving effects compared with analgesia (RR=1.11, 95% CI 0.97 to 1.26)
- acupuncture plus analgesia was more effective in reducing cancer pain than analgesic alone (MD= -0.76, 95% CI -0.14 to -0.39)

- Physical and complementary therapies can be useful as an adjunct in cancer pain management.

8. PAEDIATRIC CANCER PAIN

According to The Malaysian Society of Paediatric Haematology and Oncology, the incidence of paediatric cancer in Malaysia is about 77.4 per million in children aged <15 years old.[111] The paediatric cancer pain is quite different from the pain in adults and children respond differently to treatment.

Pain is a common symptom in children diagnosed with cancer. The pain can be tumour-related, procedure-related or treatment-related.

Tumour-related pain can present:[112]

- before or at diagnosis
- during initial treatment
- when tumour is resistant to treatment
- at disease recurrence

The following table shows examples of cancer-related pain in children.

Table 6. Examples of Cancer-related Pain in Children:[112]

Tumour-related pain	• before or at diagnosis • during initial treatment • when tumour is resistant to treatment • at disease recurrence
Procedural related pain	a. diagnostic procedures • venepuncture • lumbar puncture • bone marrow aspirate and biopsy • tissue biopsy b. Procedures • central venous line insertion • pleural or peritoneal drainage • external ventricular drainage • ventricular-peritoneal shunt • surgeries • wound dressing/debridement
Treatment-related pain	• mucositis (post-chemotherapy or radiotherapy) • acute pancreatitis (SE of chemotherapy e.g. asparaginase) • neutropenic enterocolitis • haemorrhagic cystitis (e.g. with cyclophosphamide, ifosfamide, radiotherapy) • intracranial haemorrhage (thrombocytopenia from bone marrow suppression) • peripheral neuropathic pain (e.g. with vincristine, cisplatin) • post-operative pain • phantom limb pain • procedural pain (on treatment protocol)

8.1 Principles of Pain Assessment

Pain assessment in children can be quite different than adults. The following are principles to guide pain assessment in children using the acronym **A.B.C.D.E**:

Table 7. ABC of Pain Assessment in Children[112]

A	**A**sk the child and **A**ssess pain score
B	Use **B**ehavioural and Biological measures
C	Find the **C**ause
D	**D**ecide and **D**eliver treatment in a timely manner
E	**E**valuate outcome

Assessment and management of pain in children and infants are different from adults due to:[112]

- Communication: Children have limited verbal and cognitive abilities. Non-verbal cues and observation are essential approaches to assessment.
- Development: Children have a wide physiological, cognitive, and developmental response to pain according to their age groups. This has to be carefully assessed.
- Fear and anxiety: Children are reluctant to report pain that reflect their pain experience. Managing emotions can be done through play therapy, distraction and other cognitive behaviour strategies.
- Dosage: Medication must be carefully adjusted according to age, weight and developmental understanding. Adolescent also has a unique approach to cancer pain management. Healthcare workers will require appropriate training for assessment and management.
- Parental involvement: Caregivers input is an essential component and part of the assessment.
- Ethical consideration: Children are not able to give consent for any intervention and medical management. Consent must be taken from legal caregivers or parents.

8.2 Pain Assessment Tools

The choice of a pain assessment tool should take into consideration:[112, 113]

- the child's developmental age
- verbal ability

These are shown in **Table 8** and **9**.

Table 8. Pain Assessment Tools Based on Child's Developmental Age[112]

Age	Pain rating scale
1 month to 4 years	**FLACC** • Observe the child's behaviour in 5 dimensions (Face, Legs, Arms, Cry, Consolability) for 2 to 5 minutes, and assign a score (maximum 10)
4 years to 7 years	**Revised FACES** • Picture-based scale where the child selects 1 to 6 faces to represent their pain experience
≥7 years	**Numerical rating scale** • Ask the child to assign a number to their pain, with '0' being no pain and '10' being the worst imaginable pain

Table 9. Pain Assessment Tools Based on Verbal Ability[112]

Special population	Pain rating scale
Neurological impaired	**Revised FLACC** • Incorporates individualised pain behaviours which is unique to a child
Critically ill	**COMFORT-Behaviour scale and FLACC**
Neonates	**Neonatal/Infant Pain Scale (NIPS)**

8.3 Treatment

Cancer pain in children can be effectively managed by using drugs e.g. opioids, non-opioids and adjuvant analgesics with the biopsychosocial or multi-modality approach covering physical, psychosocial and spiritual entities.

- WHO uses simple principle for analgesia in children:[112]
  - oral route is the preferred choice
  - dosing of analgesic should be at a fixed regular interval
  - WHO 3-step analgesic ladder is the proposed model

Analgesia is given based on severity of pain from mild to severe pain in the 3-step WHO ladder in children. Weak opioids still have a role despite insufficient robust data.[112]

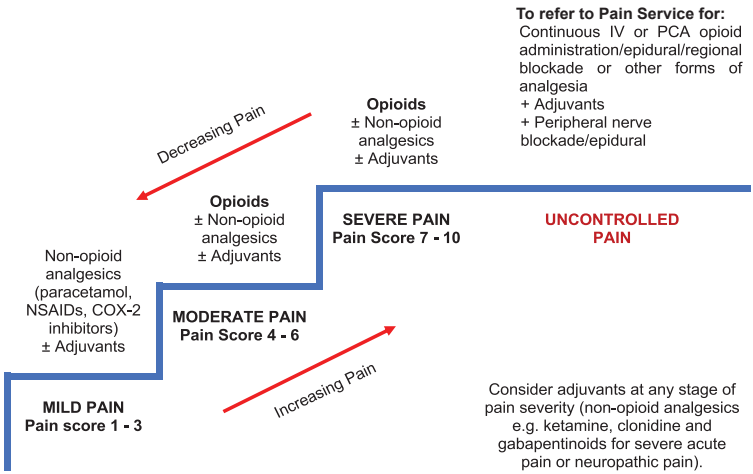


Figure 3. Modified Analgesic Ladder

Source: Ministry of Health, Malaysia. Paediatric Pain Management Guidelines 2023. Putrajaya: MoH; 2023.

In developing countries, children with cancer experience pain related to advanced disease and treatment approaches e.g. chemotherapy or radiotherapy.[114]

- **Non-opioid analgesics**

The first step in the WHO Analgesic 3-Step Ladder is non-opioid drugs, e.g. paracetamol and NSAIDs, with the optional use of adjuvants for mild pain.[112] In the second step of WHO pain ladder, non-opioid analgesics may work synergistically with opioids as co-analgesic to produce a better pain relief (refer to Figure 3).[112]

Paracetamol is generally safe but may cause hepatotoxicity if overdosed (refer to **Appendix 5b**).[115] GI ulceration, nephrotoxicity and CV events are the known AEs of NSAIDs. Thus, lowest effective dose of NSAIDs should be given with proton pump inhibitors to prevent gastro-duodenal ulcers.[116] The dosages of commonly use non-opioid analgesics are shown in **Appendix 5b**.

Recommendation 17
- Paracetamol or nonsteroidal anti-inflammatory drugs should be used in children with mild cancer pain.
- Paracetamol should be used in combination with opioids as co-analgesic unless contraindicated in children with cancer pain.

- **Opioid analgesics**

Morphine is considered in the second step of WHO 3-Step Ladder when the pain is moderate to severe in children. The minimum interval between each dose is between one to four hours. The benefits of using an effective strong opioid analgesic outweigh the benefits of weak opioids in the paediatric population when compared with the uncertainty associated with the response to codeine and tramadol. Caution on the use codeine and tramadol has been issued due to ultra metabolisers and potential AEs.[117, level III]

a. Tramadol

Tramadol is a synthetic analgesic with unpredictable effects due to its wide variability in metabolism. The drug has a ceiling effect. It is unsuitable for escalating mild-moderate pain or severe pain. It has the potential to cause side effects in children.[112]

b. Morphine

Oral morphine is the first-line therapy for severe cancer pain in children. Its effectiveness in pain relief has been extrapolated from the treatment of adult with chronic cancer pain.[112] Oral morphine is available as either IR or SR preparations. IV morphine is used for rapid onset analgesia and when the patients are unable to tolerate oral morphine.[117, level III] If the opioid requirement goes beyond 1 mg/kg/day, it is likely that the patient will require regular morphine.[113; 115] Morphine dose should be monitored after 24 - 48 hours of morphine use. Alternative routes of administration should be based on clinical judgement, drug availability and patient's preference. The initial dose of morphine and its frequency is shown in **Appendix 5b**.

Case Example for Opioid Titration in Paediatric Cancer Pain

Aiman is a 10-year-old boy with relapsed Acute Lymphoblastic Leukemia with bone metastasis. He complains of generalised pain with pain score of 6/10. He is opioid naïve with normal renal and liver function. His weight is 20kg and he is currently at home.

Method of dose calculation:

- Immediate release oral morphine 0.2 mg/kg/dose x 20 kg = 4 mg q4h (maximum initial dose is 5 mg/dose for children) = 24 mg/day

Breakthrough dose: 1/10 to 1/6 of daily dose (2.5 - 4 mg), can be served 1-2 hours after previous dose of morphine.

Recommendation 18

- Oral morphine is the preferred choice for children with moderate to severe cancer pain.

c. Fentanyl

Transdermal fentanyl is an effective alternative to oral morphine in children with difficulty in swallowing or those having intractable nausea and vomiting whose opioid requirements are stable.[115] IV fentanyl can be used in children with specific circumstances e.g. renal failure but preferably this is done under specialist care.[112] Refer to **Table 4** on suggested dose conversion ratio for conversion of oral morphine to fentanyl patch.

d. Oxycodone

Oxycodone is an alternative strong opioid which is as effective as oral morphine. Refer to **Table 4** on suggested dose conversion ratio for conversion of oral morphine to oxycodone.

Recommendation 19

- Fentanyl or oxycodone may be used as alternative analgesics in children with moderate to severe cancer pain.

e. Methadone

Methadone is only used as an alternative opioid for cancer pain in children. However, it should only be prescribed under specialist supervision in palliative care settings.[118, level III]

For opioid AEs and their management, refer to **Chapter 4.4.8**.

- **Adjuvant drugs**

Adjuvant analgesics may be used with other analgesics including strong opioids in children with cancer pain.[11] Combining drugs with different mechanisms of action improve analgesia and decrease AEs in the patients. This can be used at any stage of pain severity as per **Figure 3**. However, there is insufficient evidence on the use of adjuvant analgesics in the paediatric age group.

The use of antidepressants in children has been associated with an increased risk of suicidal ideation and behaviour.[119] However, amitriptyline has been used in the management of pain especially bone pain and neuropathic pain in children.[120, level III]

In children, neuropathic pain can be treated with anticonvulsants e.g. gabapentin, pregabalin and sodium valproate. It is important to monitor undesired AEs e.g. headache, drowsiness and ataxia when commencing these agents.[113]

Ketamine should be used by specialists familiar with cancer pain management in children. It is generally used in low doses.[115]

Corticosteroids are commonly used for children with pain related to mass effect of tumour e.g. headache from brain metastases, abdominal pain from liver capsule distension or intestinal obstruction and neuropathic pain from spinal cord compression.[121]

Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases.[120, level III; 121; 122, level III]

Refer to **Appendix 5b** on Dosage of Commonly Used Adjuvant Drugs in Children with Cancer Pain.

Recommendation 20
- Adjuvant analgesics may be considered in cancer pain management in children.

9. BARRIERS AND EDUCATION

- **Barriers**

Barriers to the effective management of cancer pain need to be identified and addressed. A systematic review found negative attitudes and a lack of knowledge towards cancer pain management among the healthcare providers, patients, family caregivers and general public. The most commonly cited barriers were fear of drug addiction, tolerance and AEs of opioids.[123, level III]

In another study on cancer pain management by family caregivers, the main challenges can be grouped into three parts:[124, level III]

- communication and teamwork issues which included caregivers' receipt of inadequate information regarding pain management and, inappropriate and ineffective communication from the healthcare team
- caregiver issues which were related to caregivers' fear and beliefs, concurrent responsibilities and, lack of pain-related knowledge and skills
- patient issues which included patient's own fear and beliefs, psychological and physiological well-being, adherence to medications and reluctance to report pain

A cross-sectional study conducted in Hospital Umum Sarawak, Malaysia showed that:[125, level III]

- among the four domains of patient-related barriers explored via BQ-II questionnaire, fatalism had the highest median BQ-II score, followed by harmful effects, physiological effects and communication
- education level, gender and marital status had significant impact on various barrier domains
- ethnicity had no significant impact on all four domains

A multinational cross-sectional survey showed:[126, level III]

- of all the attitudinal barriers, fear of addiction to opioids was the strongest barrier across all countries whereas fatalism was the weakest barrier
- barriers scores were higher in patients of older age, male gender, higher pain severity or pain interference, lower Karnofsky scores and shorter duration of opioid use

In a multicentre cross-sectional study, depression was significantly associated with total barrier score to cancer pain management. Therefore, screening and treatment of depression should be an important component of successful pain management.[127, level III]

- It is important to identify and address barriers to effective cancer pain management.

- **Education**

Education on issues related to cancer pain is an essential element to effective cancer pain management. This involves not only the patients, but also the carers, family and healthcare providers.

Educational strategies should focus on addressing the following issues:[9]

- 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)

10. FOLLOW-UP AND REFERRAL

Follow-up care for patients with cancer pain can be provided at home, primary care clinics or specialised outpatient clinics. With the advent of better internet services, teleconferencing or video call services can also be used to help patients who do not have easy access to conventional follow-up.

Two recent observational studies supported the structured outpatient follow-up of cancer patients:

- proper clinic guideline programme with a multidisciplinary approach, availability of pain interventions and palliative care referral in a specialist outpatient clinic led to significant improvement in BPI and pain score in ESAS[128, level II-3]
- physician-pharmacist joint clinic was significantly more effective than standard care in BPI pain intensity, adequacy of pain management and medication adherence[129, level II-2]

A home care service provided by community palliative care providers can reach out to patients in their own homes. This is especially important for patients who are unable to travel or have mobility issues. A Cochrane systematic review showed mixed results in the improvement in pain control between community home palliative care services and standard care.[130, level I]

In the previous local CPG on cancer pain, 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 has been recommended.[9]

There are many different types of healthcare technology that can be used in delivering patient care. Videoconferencing can help when in-person conversations are not feasible. A Cochrane systemic review on telephone interventions for adults with cancer showed limited and mixed results on pain reduction compared with usual care. The certainty of the evidence on this outcome was very low.[131, level I] In a non-randomised controlled trial, home telemonitoring significantly increased pain registration and prescription for analgesics compared with usual care in cancer patients.[132, level II-1]

In another systematic review assessing the effectiveness of mHealth applications (apps) for self-management in improving pain, psychological distress, fatigue or sleep outcomes in adult cancer survivors, three out of four studies reported improvement in pain but only one showed a significant difference in those patients using the apps compared with those not using it.[133, level I]

A meta-analysis on the effectiveness of telemedicine on pain management in patients with cancer showed it improved:[134, level I]

- pain intensity (SMD= -0.28, 95% CI -0.49 to -0.06)
- pain interference (SMD= -0.41, 95% CI -0.54 to -0.28)

According to the Cochrane Risk of Bias, the risk of bias in most studies was considered low.

A list of community palliative care providers available in Malaysia can be downloaded from the Malaysian Hospice & Palliative Care Council website (https://www.malaysianhospicecouncil.com/).

Recommendation 21

- Cancer patients should be followed-up for pain management either in the specialist outpatient clinic, primary care clinic or at home.
  - Teleconsultations and digital applications may be used for this purpose.

Although most pain experienced by the patients can be managed by the primary team, there might be pain which does not respond well to initial treatment and requires specialised care. Thus, patients with severe pain and inadequate pain management should be considered for referral to pain or palliative specialist services.[135; 136, level III]

11. IMPLEMENTING THE GUIDELINES

Implementation of this CPG is important as it helps in providing quality healthcare services based on the best and most recent available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

11.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in this CPG include:

- availability of the CPG to healthcare providers (hardcopies and softcopies/online)
- regular seminars/conferences/courses for healthcare providers on management of cancer pain including those involving professional bodies
- presence of "Pain as 5th Vital Sign" strategy and pain-free hospital concept involving multidisciplinary team
- public awareness activities that involve governmental/non-governmental organisations e.g. World Hospice and Palliative Care Day

Limiting factors in the CPG implementation include:

- limited awareness and understanding/knowledge in managing cancer pain among healthcare providers especially on the use of opioids
- variation in clinical management and preferences
- insufficient resources in terms of expertise and medications
- misconception about the disease and its management by the public

11.2 Potential Resource Implications

Appropriate assessment and treatment of cancer pain is crucial for the successful management of the condition. This includes the proper use of opioids for moderate to severe cancer pain. However, barriers to its use dampen the aims of controlling cancer pain at various level of care. These are supported by local studies on the issue and the lower rate of opioid use in the country compared with the global rate. Efforts must be improved to educate both healthcare providers and patients/carers on the judicious use of opioids in patients with cancer pain. Working together with the NGOs like hospice will facilitate the implementation of these guidelines. Certain medications like IR morphine should be made available in all primary care centres.

In line with the key recommendations of the CPG and the National Key Performance Index of Palliative Medicine, the following is proposed as clinical audit indicator for quality management of cancer pain:

$$\text{Percentage of patients with cancer pain score of 7 - 10 who are prescribed with strong opioids} = \frac{\text{Number of patients with cancer pain score of 7 - 10 who are prescribed with strong opioids in a period}}{\text{Total number of patients with cancer pain score of 7 - 10 in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effective and safe pharmacological treatments in cancer pain?

1. CANCER PAIN/
2. ((cancer or neoplasm or tumo?r) adj2 associated pain).tw.
3. ((cancer or neoplasm or tumo?r) adj2 related pain).tw.
4. ((cancer-associated or cancer-related or cancer or neoplasm-associated or neoplasm-related or tumo?r-associated or tumo?r-related) adj1 pain*).tw.
5. 1 or 2 or 3 or 4
6. (pharmaco* adj1 treatment*).tw.
7. DRUG THERAPY/
8. (drug adj1 therap*).tw.
9. pharmacotherap*.tw.
10. ANALGESICS, NON-NARCOTIC/
11. ((non-opioid or nonopioid) adj1 (analgesic* or drug*)).tw.
12. (non opioid adj2 (analgesic* or drug*)).tw.
13. ((nonnarcotic or non-narcotic) adj1 (analgesic* or drug*)).tw.
14. ACETAMINOPHEN/
15. acet#minophen.tw.
16. n-acetyl-p-aminophenol.tw.
17. paracetamol.tw.
18. ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL/
19. ((non-steroidal or nonsteroidal) adj2 (anti-inflammatory agent* or antiinflammatory agent*)).tw.
20. (nonsteroidal anti inflammatory adj3 agent*).tw.
21. (analgesic* adj1 (antiiflammatory or anti-inflammatory)).tw.
22. (non steroidal anti inflammatory adj4 agent*).tw.
23. (analgesic* adj2 anti flammatory).tw.
24. nsaid*.tw.
25. TRAMADOL/
26. tramadol.tw.
27. tramadol hydrochloride.tw.
28. TAPENTADOL/
29. tapentadol.tw.
30. tapentadol hydrochloride.tw.
31. CODEINE/
32. codeine.tw.
33. codeine phosphate.tw.
34. dihydrocodeine.tw.
35. ANALGESICS, OPIOID/

36. ((full or partial) adj2 opioid agonist*).tw.
37. (opioid adj1 analgesic*).tw.
38. (opioid mixed adj2 agonist-antagonist*).tw.
39. opioid mixed agonist antagonist*.tw.
40. opioid*.tw.
41. MORPHINE/
42. (morphine adj1 chloride).tw.
43. (ms adj1 contin).tw.
44. duramorph.tw.
45. morphine.tw.
46. (morphine adj1 (sulfate or sulphate)).tw.
47. (oramorph adj1 sr).tw.
48. OXYCODONE/
49. oxycodone.tw.
50. (oxycodone adj1 hydrochloride).tw.
51. oxycodone naloxone.tw.
52. FENTANYL/
53. fentanyl.tw.
54. (fentanyl adj1 citrate).tw.
55. atypical opioid.tw.
56. BUPRENORPHINE/
57. buprenorphine.tw.
58. (buprenorphine adj1 hydrochloride).tw.
59. NALBUPHINE/
60. nalbuphine.tw.
61. (nalbuphine adj1 hydrochloride).tw.
62. MEPERIDINE/
63. meperidine.tw.
64. (meperidine adj1 hydrochloride).tw.
65. pethidine.tw.
66. METHADONE/
67. methadone.tw.
68. (methadone adj1 hydrochloride).tw.
69. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70. 5 and 69
71. limit 70 to (english language and humans and yr=”2010-Current”)

Appendix 2

CLINICAL QUESTIONS

1. What are the principles of management of pain in patients with cancer?
2. What are the accuracy and reliability of clinical assessment tools of patients with cancer pain?
3. What are the accuracy and reliability of neuropathic pain assessment and tools in patients with cancer?
4. What are the accuracy and reliability of screening tools for comprehensive assessment of cancer pain?
5. What are the accuracy and reliability of pain assessment tools in patients with cognitive impairment/learning disabilities with cancer pain?
6. What are the principles of pharmacological treatment in cancer pain?
7. What are the effective and safe pharmacological treatments in cancer pain?
8. Are cannabinoids/medical cannabis effective and safe for treatment of cancer pain?
9. What are the prescribing, titration and maintenance issues of morphine and other strong opioids in patients with cancer?
10. What are the clinical issues related to tolerance, dependence, and addiction to opioids in patients with cancer?
11. What are the pharmacological strategies for breakthrough pain and other acute pain crises in patients with cancer?
12. What are the effective and safe adjuvant medications in cancer pain management?
13. What are the effectiveness and safety of different drug formulations and routes of administration in managing pain for patients with cancer?
14. What are the effectiveness and safety of anticancer therapies in the management of cancer pain?
15. What are the effectiveness and safety of radionuclide therapies in the management of cancer pain?
16. What are the effective and safe non-pharmacological/non-invasive treatments in cancer pain?
17. What are the effectiveness and safety of neurolytic therapies in management of cancer pain?
18. What are the effectiveness and safety of intrathecal neuraxial opioid and/or neuraxial adjuvants in refractory cancer?

19. What are the effectiveness and safety of surgery in cancer pain?
20. What are the effective and safe treatment for cancer pain in children?
21. What are the roles of multidisciplinary team/members/clinic in managing patients with cancer pain?
22. How should patients with cancer pain be followed-up?
23. What are the referral criteria of patients with cancer pain to be referred to specialist care in primary/secondary/tertiary care?

Appendix 3

SEDATION SCORE (MACINTYRE)

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.

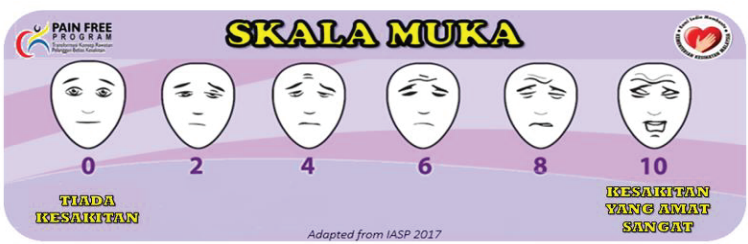
Appendix 4

ASSESSMENT TOOLS

a. Ministry of Health (MoH) Pain Scale

The MOH pain scale is a scale that combines NRS, the VAS and faces scale. The patient is asked to indicate his/ her level of pain intensity by pointing along a scale. The scale has numbers and the pain score is recorded as a number from 0 to 10.

In children less than 7 years old and cognitively impaired adults, other scales like IASP Faces Pain Scale or FLACC scale can be used. In patients who are sedated and intubated, pain assessment will rely on observations and behavioral assessment.



Source: Ministry of Health, Malaysia. Pain as the 5th Vital Sign Guideline: 3rd Edition. Putrajaya: MoH; 2018.

b. FLACC Scale

This is an observational score, and is used for paediatric patients aged >1 month to 3 years. It may also be used in adult patients who are unable to communicate verbally, e.g. very elderly patients, cognitively impaired patients.

1. Observe behaviour
2. Select a score according to behaviour
3. Add the scores for the total

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

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, distractible	Difficult to console

Source: Ministry of Health, Malaysia. Pain as the 5th Vital Sign Guideline: 3rd Edition. Putrajaya: MoH; 2018.

c. Verbal Rating Scale (VRS)

No pain	**0**
Mild pain	**1**
Moderate pain	**2**
Severe pain	**3**
Very severe pain	**4**

The VRS consists of a list of adjectives describing different levels of pain intensity. Patients are asked to select the adjective that best represents their pain. This should reflect the extremes of this dimension; from 'no pain' to 'very severe pain' and sufficient intervening adjectives to capture gradations of pain intensity that may be experienced between extremes. VRSs are scored as above but these are ranks, not equal intervals.

Adapted: Outcome measures. The Faculty of Pain Medicine of the Royal College of Anaesthetists. 2019.

d. Short-form McGill Pain Questionnaire (SF-MPQ-2)

Date: _____
Subject ID: _____

For this questionnaire, I will provide you a list of words that describe some of the different qualities of pain and related symptoms. Please rate the intensity of each of the pain and related symptoms you felt during the past week on 0 to 10 scale, with 0 being no pain and 10 being the worst pain you can imagine. Use 0 if the word does not describe your pain or related symptoms. Limit yourself to a description of the pain related to your surgery or pelvic pain.

1.	**Throbbing pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2.	**Shooting pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3.	**Stabbing pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4.	**Sharp pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5.	**Cramping pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6.	**Gnawing pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7.	**Hot-burning pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8.	**Aching pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9.	**Heavy pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10.	**Tender**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11.	**Splitting pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12.	**Tiring-exhausting**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13.	**Sickening**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14.	**Fearful**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15.	**Punishing-cruel**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16.	**Electric-shock pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17.	**Cold-freezing pain**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18.	**Piercing**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19.	**Pain caused by light touch**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20.	**Itching**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21.	**Tingling or 'pins and needles'**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22.	**Numbness**	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

23. **Present Pain Intensity (PPI)** - Numerical Pain Rating Scale. On a scale from zero to ten, zero indicating no pain and ten indicating worst pain imaginable, rate your pelvic pain:

none	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

24. **Evaluate overall intensity of total pain experience. Please check (✓) the word that describes the pain in your pelvic area only.**

☐ *No pain* ☐ *Mild* ☐ *Discomforting* ☐ *Distressing* ☐ *Horrible* ☐ *Excruciating*

The SF-MPQ-2 consists of 24 different descriptors of pain of which each item is rated on a scale of 0-10. The scale of 0 equals to no pain and the scale of 10 equals to the worst ever pain experience during last week. The total score is calculated by summing all 24 scores.

Adapted: Melzack, Ronal. The short-form McGill pain questionnaire. Pain. 1987: 30 (2) :191-197.

e. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale

Name_____ **Date**_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensation in your skin? Works like pricking, tingling, pins and needles might describe these sensations.

a) NO – my pain doesn't really feel like this……(0)
b) YES – I get these sensations quite a lot……(5)

2) Does your pain make the skin in the painful area look different from normal? Words like motthled or looking more red or pink might describe the appearance.

a) NO – My pain doesn't affect the colour of my skin……(0)
b) YES – I've noticed that the pain does make my skin look different from normal…..(5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO – My pain doesn't make my skin abnormally sensitive in that area……(0)
b) YES – I've noticed that the pain does make my skin look different from normal…..(3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe the sensations.

a) NO – My pain doesn't really fell like this……(0)
b) YES – I get these sensations quite a lot……(2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations.

a) NO – I don't really get these sensations……(0)
b) YES – I get these sensations quite a lot……(1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO, normal sensation in both areas……(0)
b) YES, allodynia in painful area only……(5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin-prink is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none/blunt only (raised PPT) or a vary painful sensation (lowered PPT), an altered PPT is present.

If a pin-prick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas……(0)
b) YES, altered PPT in painful area……(3)

SCORING:

Add values in parentheses for sensory description and examination finding to obtain overall score.

TOTAL SCORE (maximum 24)……

If score <12, neuropathic mechanisms are unlikely to be contributing to the patient's pain
If score >12, neuropathic mechanisms are likely to be contributing to the patient's pain

The LANSS identifies patients with neuropathic pain by combining the score of a patient's verbal description of pain and the results of neurological examination. This tool has two parts-a patient completed section and a brief physical assessment. Five questions in the patient-completed section (maximum score 16) identify those who are experiencing phenomena associated with neuropathic pain: 'pins and needles' (paraesthesia); 'red skin' (autonomic changes); 'sensitive skin' (evoked dysaesthesia); 'electric shock pain'; and 'burning pain' (spontaneous dysaesthesia). The physical assessment (maximum score 8) is designed to identify allodynia by stroking cotton wool over the painful and the anatomically equivalent non-painful area, and altered pinprick threshold (PPT) by use of a 23-gauge needle to assess perception of pinprick in the same areas.

Adapted: The LANSS Pain Scale

f. PainDETECT Questionnaire

Date: **Patient:**

How would you assess your **pain** now, at this moment?

none max.

How strong was the **strongest** pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

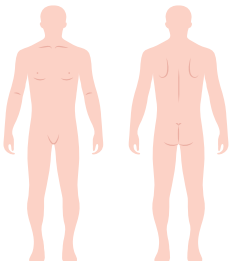
How strong was the pain during the past 4 weeks on **average**?

0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain:

- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐



Does your pain radiate to other regions of your body?

Yes ☐ No ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the areas of your pain (like crawling ants or electrical tingling)?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?
never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly notice	slightly	moderately	strongly	very strongly
x 0 =	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Total Score ☐ **out of 35**

Please transfer the total score from the pain questionnaire:
Total Score ____

Please add up the total following numbers, depending on the marked pain behaviour and the pain radiation. Then total up the final score:


Persistent pain with slight fluctuations — 0


Persistent pain with pain attacks — -1 if marked, or


Pain attacks without pain between them — +1 if marked, or

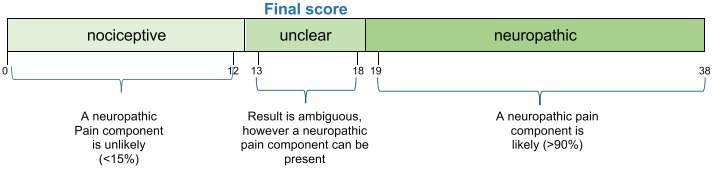

Pain attacks with pain between them — +1 if marked

Radiating pains? — +2 if yes

Final Score ____

Screening Result

Final score



The painDETECT questionnaire consists of seven questions that address the quality of neuropathic pain symptoms; it is completed by the patient and no physical examination is required. The first five questions ask about the gradation of pain, scored from 0 to 5 (never = 0, hardly noticed = 1, slightly = 2; moderately = 3, strongly = 4, very strongly = 5). Question 6 asks about the pain course pattern, scored from −1 to 2, depending on which pain course pattern diagram is selected. Question 7 asks about radiating pain, answered as yes or no, and scored as 2 or 0 respectively. The final score between −1 and 38, indicates the likelihood of a neuropathic pain component. A score of ≤ 12 indicates that pain is unlikely to have a neuropathic component (< 15%), while a score of ≥ 19 suggests that pain is likely to have a neuropathic component (> 90%).

Adapted: painDETECT Questionnaire.

g. Doeleur Neuropathique en 4 (DN4) Scale

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:
Does the pain have one or more of the following characteristics?

	YES	NO
Burning	☐	☐
Painful cold	☐	☐
Electric shocks	☐	☐

QUESTION 2:
Is the pain associated with one or more of the following symptoms in the same area?

	YES	NO
Tingling	☐	☐
Pins and needles	☐	☐
Numbness	☐	☐
Itching	☐	☐

EXAMINATION OF THE PATIENT

QUESTION 3:
Is the pain located in an area where the physical examination may reveal one or more of the following characterictics?

	YES	NO
Hypoesthesia to touch	☐	☐
Hypoesthesia to pinprick	☐	☐

QUESTION 4:
Is the painful area, can the pain be caused or increased by:

	YES	NO
Brushing?	☐	☐

YES = 1 point
NO = 0 point

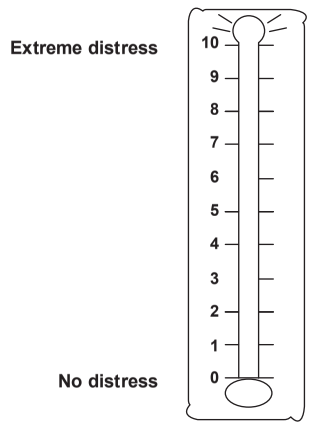
Patient's Score: /10

DN4 is a test for diagnosing neuropathic pain. It consists of 7 items related to symptoms and 3 related to clinical examination. The total DN4 score ranges from 0 to 10, and a score ≥ 4 indicates a diagnosis of peripheral neuropathic pain. The scores are added and a score of 4 or more out of 10 is suggestive of neuropathic pain.

NCCN DISTRESS THERMOMETER

Distress is an unpleasant experience of a mental, physical, social, or spiritual nature. It can affect the way you think, feel, or act. Distress may make it harder to cope with having cancer, its symptoms or its treatment.

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



PROBLEM LIST

Have you had concerns about any of the items below in the past week, including today? (Mark all that apply)

Physical Concerns
- ❑ Pain
- ❑ Sleep
- ❑ Fatigue
- ❑ Tobacco use
- ❑ Substance use
- ❑ Memory or concentration
- ❑ Sexual health
- ❑ Changes in eating
- ❑ Loss or change of physical abilities

Emotional Concerns
- ❑ Worry or anxiety
- ❑ Sadnesss or depression
- ❑ Loss of interest or enjoyment
- ❑ Grief or loss
- ❑ Fear
- ❑ Loneliness
- ❑ Anger
- ❑ Changes in appearance
- ❑ Feelings of worthlessness or being a burden

Social Concerns
- ❑ Relationship with spouse or partner
- ❑ Relationship with children
- ❑ Relationship with family members
- ❑ Relationship with friends or coworkers
- ❑ Communication with healthcare team
- ❑ Ability to have children
- ❑ Prejudice or discrimination

Practical Concerns
- ❑ Taking care of myself
- ❑ Taking care of others
- ❑ Work
- ❑ School
- ❑ Housing
- ❑ Finances
- ❑ Insurance
- ❑ Transportation
- ❑ Child care
- ❑ Having enough food
- ❑ Access to medicine
- ❑ Treatment decisions

Spiritual or Religious Concerns
- ❑ Sense of meaning or purpose
- ❑ Changes in faith or beliefs
- ❑ Death, dying or afterlife
- ❑ Conflict between beliefs and cancer treatments
- ❑ Relationship with the sacred
- ❑ Ritual or dietary needs

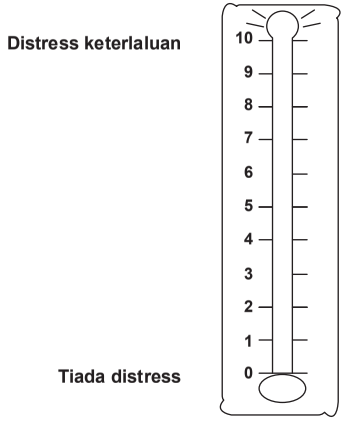
Other Concerns:

_____
_____
_____

TERMOMETER DISTRES NCCN

Distres merupakan satu pengalaman yang tidak menyenangkan, yang bersifat mental, fizikal, sosial atau spiritual. Distres boleh menjejaskan cara anda berfikir atau bertindak, atau perasaan anda. Distres boleh membuatkan seseorang berasa lebih sukar untuk menangani penyakit kanser, gejala-gejalanya, ataupun rawatannya.

Arahan: Sila bulatkan nombor (0-10) yang paling tepat menerangkan keadaan distress yang anda alami dalam tempoh seminggu yang lalu termasuk hari ini.



SENARAI MASALAH

Adakah anda mempunyai kebimbangan tentang mana-mana item di bawah dalam tempoh seminggu yang lalu, termasuk hari ini? (Tandakan semua yang berkenaan)

Kebimbangan Fizikal
- ❑ Kesakitan
- ❑ Tidur
- ❑ Kelesuan
- ❑ Penggunaan tembakau
- ❑ Penggunaan bahan terlarang
- ❑ Daya ingatan atau penumpuan
- ❑ Kesihatan seksual
- ❑ Perubahan dalam pemakanan
- ❑ Kehilangan atau perubahan keupayaan fizikal

Kebimbangan Emosi
- ❑ Kerisauan atau keresahan
- ❑ Kesedihan atau kemurungan
- ❑ Kehilangan minat atau keseronokan
- ❑ Kehibaan atau kehilangan seseorang
- ❑ Ketakutan
- ❑ Kesunyian
- ❑ Kemarahan
- ❑ Perubahan dalam penampilan
- ❑ Rasa tidak berguna atau menyusahkan

Kebimbangan Sosial
- ❑ Hubungan dengan pasangan
- ❑ Hubungan dengan anak-anak
- ❑ Hubungan dengan ahli keluarga
- ❑ Hubungan dengan kawan-kawan atau rakan sekerja
- ❑ Hubungan dengan pasukan penjagaan kesihatan
- ❑ Komunikasi dengan pasukan penjagaan kesihatan
- ❑ Keupayaan mendapat anak

Kebimbangan Praktikal
- ❑ Menjaga diri sendiri
- ❑ Menjaga orang lain
- ❑ Pekerjaan
- ❑ Sekolah
- ❑ Perumahan
- ❑ Kewangan
- ❑ Insurans
- ❑ Pengangkutan
- ❑ Penjagaan anak
- ❑ Kecukupan makanan
- ❑ Akses kepada ubat-ubatan
- ❑ Keputusan rawatan

Kebimbangan Spiritual atau Keagamaan
- ❑ Maksud dan tujuan hidup
- ❑ Perubahan kepercayaan atau pegangan
- ❑ Kematian, akan mati atau selepas mati
- ❑ Konflik antara kepercayaan dan rawatan kanser
- ❑ Hubungan dengan Tuhan
- ❑ Ritual atau keperluan pemakanan

Kebimbangan Lain:

_____
_____
_____

j. Integrated Palliative Care Outcome Scale (IPOS)

IPOS Patient Version

Name: _____

Date (dd/mm/yyyy): _____

Please write clearly, one letter or digit per box. Your answers will help us to keep improving your care and the care of others.

Thank you.

Q1. What have been your main problems or concerns over the past week?

1. _____

2. _____

3. _____

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	*Slightly*	*Moderately*	*Severely*	*Overwhelmingly*
Pain	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Shortness of breath	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Weakness or lack of energy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Nausea (feeling like you are going to be sick)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Vomiting (being sick)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Poor appetite	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Constipation	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Sore or dry mouth	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Drowsiness	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Poor mobility	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.

1. _____	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
2. _____	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
3. _____	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q4. Have any of your family or friends been anxious or worried about you?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q5. Have you been feeling depressed?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

	Always	*Most of the time*	*Sometimes*	*Occasionally*	*Not at all*
Q6. Have you felt at peace?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
Q8. Have you had as much information as you wanted?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

	Problems addressed/ No problems	*Problems mostly addressed*	***Problems partly addressed***	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

		On my own	*With help from a a friend or relative*	*With help from a member or staff*
Q10. How did you complete this questionnaire?		☐	☐	☐

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse.

IPOS (Integrated Palliative care Outcome Scale) is a measure of symptoms and concerns which matter to a patient. There are 10 questions scored on a scale of 1-4, which assess a patient's symptoms and needs with regards to physical, social, psychological and spiritual.

Adapted: IPOS Patient Version.

k. The Edmonton Symptom Assessment System (ESAS) Tool

Name:_____ **Phone Number:** _____
Address:_____ **Completed By:**_____

Please circle a number that best describes how you feel:

Please circle a number that best describes how you feel:
0 1 2 3 4 5 6 7 8 9 10

No pain **Worst possible pain**
0 1 2 3 4 5 6 7 8 9 10

Not tired **Very tired**
0 1 2 3 4 5 6 7 8 9 10

No nausea **Very nauseous**
0 1 2 3 4 5 6 7 8 9 10

Not depressed **Very depressed**
0 1 2 3 4 5 6 7 8 9 10

Calm **Very anxious**
0 1 2 3 4 5 6 7 8 9 10

Not drowsy **Very drowsy**
0 1 2 3 4 5 6 7 8 9 10

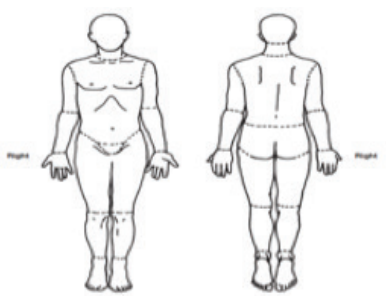
Normal appetite **No appetite**
0 1 2 3 4 5 6 7 8 9 10

Best feeling of well-being **Worst possible feeling of well-being**
0 1 2 3 4 5 6 7 8 9 10

No shortness of breath **Very short of breath**
0 1 2 3 4 5 6 7 8 9 10

Other problem

Please mark on these pictures where you feel pain or discomfort.



The ESAS is a comprehensive, yet brief and practical self-reporting tool of symptom severity (intensity) for nine common symptoms of advanced cancer (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, shortness of breath), with the option of adding a tenth patient-specific symptom. The time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that the symptom is absent and 10 that it is of the worst possible severity.

Adapted: The Edmonton Symptom Assessment System (ESAS) Tool.

I. Pain Assessment in Advanced Dementia (PAINAD) Scale

Item*	0	1	2	Score
Breathing independent of vocalisation	Normal	Occasional laboured breathing. Short period of hyperventilation.	Noisy laboured breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low-level speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying.	
Facial expression	Smiling or inexpressive	Sad. Frightened. Frown.	Facial grimacing.	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch.	Unable to console, distract or reassure.	
			Total**	

*Five-item observational tool (see the description of each item below).

**Total scores range from 0 to 10 (based on a scale of 0 to 2 for five items), with a higher score indicating more severe pain (0="no pain") to 10="severe pain")

The PAINAD scale is a reliable pain assessment tool for patients with advanced dementia. It assesses five behaviors: breathing, negative vocalisation, facial expression, body language, and the ability to be consoled. Each of the five indicators is scored on a range from 0 (not present) to 2 (completely present) based on direct observation for a total score that ranges from 0 to 10.

Reference: Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc. 2003;4(1):9-15.

Appendix 5

a. SUGGESTED MEDICATION DOSAGES AND ADVERSE EFFECTS IN ADULTS

Drug	Recommended Dosages	Side Effects	Remarks
Paracetamol	0.5 - 1 g, 6-8-hourly Max: 4 g/day	Rare	Consider dose reduction in hepatic impairment.
Non-Selective NSAIDs			
Diclofenac Sodium	50 - 150 mg daily, 8-12 -hourly Max: 150 mg/day	• Peptic ulcer • GI bleed • Platelet dysfunction • Renal impairment • Cardiac events	Use the lowest efficacious dose for the shortest possible duration. Consider dose reduction in renal impairment. Higher doses increase the risk of gastrointestinal and cardiovascular complications.
Mefenamic Acid	250 - 500 mg, 8-hourly Max: 1500 mg/day		
Ibuprofen	200 - 400 mg daily, 8-hourly Max: 2400 mg/day		
Selective NSAIDs			
Celecoxib	200 - 400 mg, 12 - 24-hourly Max: 400 mg/day	• Renal impairment • Cardiac events	Use the lowest efficacious dose for the shortest possible duration. Consider dose reduction in renal impairment and cardiovascular disease. Higher doses increase the risk of gastrointestinal and cardiovascular complications.
Etoricoxib	60 - 90 mg daily Max: 120 mg/day		
Weak Opioids			
Tramadol	50 - 100 mg, 6 - 8-hourly Max: 400 mg/day	• Drowsiness • Dizziness • Nausea • Vomiting • Constipation	Consider dose reduction in renal impairment.
Dihydrocodeine tartrate	30 - 60 mg, 6 - 8-hourly Max: 240 mg/day		
Combination Medications			
Paracetamol 500 mg + codeine 8 mg	1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day	• Drowsiness • Dizziness • Nausea • Vomiting • Constipation	Consider dose reduction in renal impairment and hepatic impairment.
Paracetamol 325 mg + tramadol 37.5 mg	1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day		
Strong Opioids			
Morphine	Starting dose (oral): 3 - 5 mg 4-hourly of IR morphine SR oral morphine: to be given in 12-hourly dosing	• Drowsiness • Dizziness • Nausea • Vomiting • Constipation	No max dose in cancer pain. Transdermal fentanyl can only be used when opioid requirements are stable, and never in an opioid naïve patient.
Oxycodone	Starting dose (oral): 5 mg of IR 4 - 6-hourly CR oxycodone: to be given in 12-hourly dosing		
Transdermal fentanyl	Equianalgesic dose of total 24 hours opioid requirement (refer to **Table 4** on conversion of opiods)		

Drug	Recommended Dosages	Side Effects	Remarks
Sublingual fentanyl	Starting dose: 100 mcg May be titrated up to 800 mcg/ episode of breakthrough pain For each episode of breakthrough pain, a second sublingual fentanyl tablet may be taken after 15-30 mins if there is inadequate pain relief (No further doses can be given. Inadequate pain relief after this dose would require other IR opioids). There is a lockout period of 2 hours before breakthrough pain can be treated again using sublingual fentanyl. Max: 2 doses/breakthrough pain episode; And 4 episodes of breakthrough pain within 24 hours	• Drowsiness • Dizziness • Nausea	The effectiveness and safety of doses above 800 mcg have not been evaluated. Oral mucositis or dry mouth may affect absorption.
Antidepressants			
Amitriptyline	Start with 12.5 - 25 mg ON Max: 150 mg/day	Anticholinergic effects e.g. dry mouth, drowsiness, urinary retention, arrhythmias, QT prolongation	Max dose seldom required. Usual effective dose 25 - 75 mg ON. Use with caution in the elderly and patients with cardiac disease, glaucoma, renal impairment and seizure risk.
Duloxetine	30 - 60 mg/day Max: 120 mg/day	• Bleeding risk • Hepatotoxicity (at higher doses) • Gastrointestinal disorder	Usual effective dose 60mg/day. Use with caution in patients with renal impairment and seizure risk.
Anticonvulsants			
Gabapentin	Start with 300 mg ON and increase by 300 mg/24 hrs every 2-3 days if necessary Max: 3600 mg/day	• Drowsiness, • dizziness, • amnesia, dry mouth tremor	Dose adjustment is required in renal impairment. Usual effective dose ≥ 600mg TDS
Pregabalin	50 - 150 mg BD Max dose: 300mg BD		Dose adjustment is required in renal impairment.
Bone Targeting Agents			
Zoledronic Acid	4 mg as a single IV infusion over 15 mins Can only be repeated after 7 days if response is inadequate	• Transient pyrexia & flu-like symptoms • Fatigue • Nausea • Osteonecrosis of the jaw	Consider dose reduction in renal impairment.

Drug	Recommended Dosages	Side Effects	Remarks
Pamidronate	30 - 90 mg as a single IV infusion over 2 - 4 hours Can only be repeated after 7 days if response is inadequate		
Denosumab	120 mg every 4 weeks	• Arthralgia • Fatigue • Hypocalcemia • Osteonecrosis of the jaw	
Corticosteroid			
Dexamethasone	8 - 16 mg/day (initial) Then reduce to lowest possible dose (usually 2mg/day)	• Bleeding • Susceptibility to infections • Impaired glycaemic control • Delirium & sleep disturbances	Try to give earlier in the day to minimise insomnia.
Laxatives			
Lactulose	15 - 20 ml orally, 6 - 8- hourly	• Bloating • Epigastric pain • Flatulence • Nausea • Vomiting • Cramping • Abdominal distension Nausea • Diarrhoea	May be mixed with fruit juice, water or milk. Reasonable fluid intake is required for effectiveness
Macrogol	1 - 4 sachets/day		Reasonable fluid intake is required for effectiveness
Bisacodyl	5 - 10 mg orally, 1 - 2 times daily Max: 20 mg/day	• Diarrhoea • Nausea • Vomiting • Rectal • irritation • Abdominal cramps • Bloating	Enteric coated tablet and should not be crushed. Exercise caution in GI obstruction, perforation or severe impaction.
Senna	2 tabs OD or 1 tab BD Max: 8 tabs/day	• Diarrhea • Nausea • Abdominal cramps	Exercise caution in GI obstruction, perforation or severe impaction.
Antiemetics			
Metoclopramide	10 - 20 mg, 6 - 8 hourly	• Extrapyramidal reactions • Dizziness • Drowsiness	Consider dose reduction in renal impairment.
Prochlorperazine	10 - 30 mg daily in divided doses		
Haloperidol	0.5 - 3 mg single dose nocte	• Extrapyramidal symptoms • Prolonged QT interval	

Adapted:

1. Wilcock A. Howard P, Charlesworth S. Palliative Care Formulary. Seventh Edition. London: Pharmaceutical Press; 2020.
2. Cherny NI, Fallon MT, Kaasa S, et al. Oxford Textbook of Palliative Medicine. Oxford: Oxford University Press; 2021.
3. Guidelines Review Committee. (2019). WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Available at: https://www.who.int/publications/i/item/9789241550390)

b. SUGGESTED MEDICATION DOSAGES IN PAEDIATRICS

Drug			Route	1 month-2 years	2 - 12 years	12 - 18 years
				Dose and frequency		
Non-opioids analgesics	Paracetamol		Oral	**0 - 3 months:** 15 mg/kg 6 - 8 H (Max: 60 mg/kg/day; if preterm 28 - 32 CGA, max 30 mg/kg/day) **>3 months -** 12 years: 15 mg/kg 4 - 6 H (Max: 75 mg/kg/day or 4 g/day)		500 mg - 1 g 4 - 6 g (if non-obese ≥50 kg: 1 g 4 -6H) (Max: 4 g/day)
			Per rectal	**0 - 3 months: LD**: 30 mg/kg; **MD**: 20 mg/kg 8 H (Max: 60 mg/kg/day) **>3 month - 12 years: LD**: 40 mg/kg; **MD**: 15 - 20 mg/kg 6 H (Max: 75 mg/kg/day)		
			IV	**Preterm neonate over 32/52 CGA**: 7.5 mg/kg 8 H (Max 25 mg/kg/day) **Term neonate & until 10 kg:** 7.5 mg/kg 6 - 8H (Max: 30 mg/kg/day) **>10 kg or child up to 50 kg:** 15 mg/kg 4 - 6H (Max: 60 mg/kg/day, not exceeding 2 g/day if <33 kg, or 3 g/day for 33 - 50 kg)		**If non-obese** >50 kg: 1 g 4 - 6H (Max: 4 g/day) ****Obese Children:** 15 mg/kg adjusted body weight (Max: 4 g/day)
	NSAIDs	Ibuprofen	Oral	**<3 months:** not recommended **>3 months:** 5 mg/kg 6 - 8 H (Max: 20 mg/kg/day) **6 months - 12 years**: 5 -10 mg/kg 6 - 8 H (Max: 30 - 40 mg/kg/day or 1.2 g/day, whichever is less)		200 mg - 400 mg 4 – 6 H (Max: 2.4 g/day)
		Diclofenac	Oral	**<6 months:** not recommended **>6 months or >10 kg:** 0.3 - 1 mg/kg 8 H (Max: 3 mg/kg/day up to 150 mg/day, whichever is less for 2 days)		Oral 25 - 50 mg 8 H (Max: 3 doses/day)
			Per rectal	**> 1 year:** 1 mg/kg 8 - 12H (Max: 3 mg/kg/day up to 150 mg/day, whichever is less)		50 - 100 mg (oral to be started 18 H after initial 100 mg suppository)
	COX-2 inhibitors	Celecoxib	Oral	**<2 years:** not recommended	**>2 years:** weigh risks and benefits **10 - 25 kg:** 50 mg 12 H **>25 kg:** 100 mg 12 H	
		Parecoxib	IV	**<2 years:** not recommended	**>2 years:** weigh risks and benefits A single dose of 0.5 -1 mg/kg (Max: 40 mg, administered by the anaesthetists in theatres. NSAIDs should only be administered 24 H after a dose of parecoxib.)	
	Fentanyl		IV	**For specialist use /with supervision only.** Bolus: 1 - 2 mcg/kg/dose (Should only be given by the Anaesthetists/PICU Team/Paediatric Emergency Specialist/ Trained accredited personnel) INFUSION in an independent line (in ICU): **Preparation:** Dilute 20 mcg/kg of fentanyl in 50 ml normal saline. 1 ml of solution= 0.4 mcg/kg of fentanyl Suggested rate: 0.5 - 2 ml/H (Max: 4 ml/H) (0.2 - 0.8 mcg/kg/H)		
			PCA	(Restricted to Pain Service) **Initial PCA dosing:** Concentration: 0.4 mcg/ml; Bolus dose: 0.4 - 0.8 mcg/kg; Lockout interval: 5 to 7 minutes. Basal infusion (optional): 0 - 0.8 mcg/kg; 4 H limit - 4 mcg/kg		
	Tramadol		Oral/IV	**>1 year:** 0.5 - 1 mg/kg 4 - 6 H (with caution or refer Pain Service) **NB:** For tonsillectomy, max 1 mg/kg/dose 6 - 8 H (caution in OSA)		**>12 years:** 1 mg/kg 4 - 6 H (Max: 100 mg/dose or 400 mg/day)

Drug		Route	1 month-2 years	2 - 12 years	12 - 18 years
			Dose and frequency		
	Oxycodone	Oral	**> 1 month:** IR 0.1 - 0.2 mg/kg (Max 5 mg) PRN or 4 - 6H (by APS/ Palliative team) **NB:** IR for acute pain; SR for severe background pain (only available in tablet)		
	Morphine	Oral	**> 1 month - 1 year:** 0.1 mg/kg 4 - 6 H (for moderate - severe pain) (use with caution) **> 1 year:** 0.1 - 0.2 mg/kg 4 - 6 H (for moderate pain) 0.2 - 0.4 mg/kg 4 - 6 H (for severe pain)		**>12 years:** 0.1 - 0.3 mg/kg 4 - 6 H (Max: 10 - 15mg/dose, up to 6 times/24 H)
		SC	0.1- 0.2 mg/kg **<6 months:** (up to 4 times/24H) **>6 months:** (up to 6 times/24H)	0.2 mg/kg (up to 6 times/24 H)	**>12 years:** 5 - 10 mg (up to 6 times/24 H)
		IV	**BOLUS:** **Slow titration: Refer IV morphine titration protocol 1-12 months:** Max: 0.1 mg/kg (up to 4 times/24 H) **>1 year**: Max: 0.1 mg/kg (up to 6 times/ 24 H)		**BOLUS:** Slow titration: **Refer IV morphine titration protocol** **>12 years:** 2.5 - 10 mg (up to 6 times/24 H)
			INFUSION in an independent line (with caution): **Preparation**: Dilute 0.5 mg/kg of morphine (Max: 50 mg) in 50 ml normal saline. 1 ml of solution = 10 mcg/kg of morphine **Suggested rate:** **Neonates:** 0.5 - 0.7 ml/H (Max: 1 ml/H) (5 - 10 mcg/kg/H) **1 - 3 months:** 0.5 - 1 ml/H (Max: 2 ml/H) (5 - 20 mcg/kg/H) **>3 months:** 1 - 2ml/H (Max: 4ml/H) (10 - 40 mcg/kg/H)		
		PCA	**Initial PCA dosing: (Restricted to APS team)** Concentration: 10 - 20 mcg/ml; Bolus dose: 10 - 20 mcg/kg; Lockout interval: 5 to 7 minutes. Basal infusion (optional): 0 - 20 mcg/kg/H; 4 H limit 300 mcg/kg		
	Naloxone	IV	0.01 mg/kg IV (Max: 0.4 mg) may repeat every 2 minutes		
Adjuvants	**Ketamine**	Oral	Oral: 2 - 10 mg/kg (sedation pre-medication)		
		IV	**BOLUS for analgesia:** 0.2 - 0.5 mg/kg; **for sedation:** 1 - 1.5 mg/kg (use restricted to trained personnel only) **INFUSION in an independent line:** (use restricted to trained personnel only) **Preparation:** Dilute 5 mg/kg of ketamine (Max: 250 mg) in 50 ml normal saline. 1 ml of solution= 100 mcg/kg of ketamine Suggested rate: 0.2 - 2 ml/H (Max: 4 ml/H) (20 - 400 mcg/kg/H)		
	Clonidine	Oral	**Analgesic adjunct:** 1 - 2 mcg/kg PRN or 8 H **sedation premedication:** 2 - 4 mcg/kg **NB:** antihypertensive - do not give if hypotensive		
		IV	1 - 2 mcg/kg PRN or 8H **(with caution)** **NB:** antihypertensive - do not give if hypotensive		
	Gabapentin	Oral	Initial dose: 5 mg/kg ON, increase if required to 5 mg/kg 12H (Day 2), then 5 mg/kg 8H (Day 3)		
Local Anaesthetics	**Lignocaine**	LA/RA	Max dose: 4 - 5mg/kg		
	Levobupivacaine/Bupivacaine	LA/RA	Max dose: **Neonates - <6 months**: 1.5 - 2 mg/kg; **>6 months:** 2 - 2.5 mg/kg **NB:** bupivacaine is particularly cardiotoxic		
		Epidural infusion	**Levobupivacaine 0.1% ± fentanyl infusion:** (restricted to APS team) **Preparation:** Dilute 10 ml of levobupivacaine/bupivacaine 0.5% (i.e., 50 mg) in 50 ml normal saline + fentanyl **(<1 months**: Nil; **1 months - 1 year:** fentanyl 1 mcg/ml; **>1 year:** fentanyl 2 mcg/ml) Suggested rate: **Neonates:** levobupivacaine 0.1%: 0.1 - 0.2 ml/kg/H		

Drug		Route	1 month-2 years	2 - 12 years	12 - 18 years
			Dose and frequency		
			1 months - 1 year: levobupivacaine 0.1% + fentanyl 1 mcg/ml: 0.2 - 0.4 ml/kg/H **>1 year:** levobupivacaine 0.1% + fentanyl 2 mcg/ml: 0.2 - 0.4 ml/kg/H		
	Ropivacaine	LA/RA	Max dose: **Neonates - <6 months:** 1.5 - 2 mg/kg; **>6 months:** 2 - 3 mg/kg		
			Ropivacaine 0.1% ± fentanyl infusion: (restricted to APS team) Preparation: Dilute 25 ml of ropivacaine 0.2% (i.e., 50 mg) in 50 ml normal saline or dilute 6.7 ml of ropivacaine 0.75% (i.e., 50 mg) in 50 ml NS + fentanyl **(<1months:** Nil; **1 month - 1 year:** fentanyl 1 mcg/ml; **>1 year:** fentanyl 2 mcg/ml) **Suggested rate: Neonates:** ropivacaine 0.1%: 0.1 - 0.2 ml/kg/H **1 month - 1 year:** ropivacaine 0.1% + fentanyl 1 mcg/ml: 0.2 - 0.4 ml/kg/H **>1year:** ropivacaine 0.1% + fentanyl 2 mcg/ml: 0.2 - 0.4 ml/kg/H		

CGA: corrected gestational age; IR: immediate release; IV: intravenous; LA: local infiltration; NB: newborn; OSA: obstructive sleep apnoea; SC: subcutaneous; SR: slow release; PCA: patient-controlled analgesia; RA: regional anaesthesia; H: hour; Max: maximum; LD: loading dose; MD: maintenance dose; IBW: ideal body weight, ON: on night

****For Obese Children, recommended adjustments for drug dosing**:
Opioids: Ideal Body weight (IBW);
Paracetamol and NSAID: Adjusted Body Weight=IBW+ 0.4 x (Actual BW - IBW)

Adapted: Ministry of Health, Malaysia. Paediatric Pain Management Guidelines 2023. Putrajaya: MoH; 2023.

Appendix 6

GUIDE FOR TRANSDERMAL FENTANYL USE

Step 1: Preparation of the skin

- Ensure that the skin is completely dry and clean before applying the patch. Use only water to wash the skin. Do not apply soap, cream, oil or ointment on the area.
- Do NOT apply the patch over your Totally Implantable Venous Catheter (e.g. chemoport)/over a joint area/on irradiated skin.
- Body hair should be clipped with scissors IF necessary and NOT shaved.

Step 2: Preparation of patch

- Each patch is sealed in its own sachet. Tear or cut open the sachet at the notch/arrow. Do NOT cut across the middle of the sachet.

Step 3: Method of administration

- Peel one half of the plastic backing away from the centre of the patch. Try not to touch the sticky side of the patch. Press the sticky part of the patch onto the skin.
- Remove the other half of the plastic backing and press the whole patch onto the skin. Hold for 30 seconds. Make sure it sticks well, especially the edges.
- Change the patch every 72 hours. Remove the old patch before applying a new one. The date and time of patch due change should be written on the patch.
- Do NOT apply the patch on the same place twice in a row. Change the site of application to allow the skin to rest.
- If you need to apply more than one patch at a time, place the patches adequately apart so that the edges do not touch or overlap each other.
- If the patch falls off/peels off before the date and time of due change, apply a new patch on a new area of skin.

Step 3: Disposal of used patch

- Fold used patch in half with the adhesive side inwards.
- Discard in clinical waste bin (in the hospital) or in a waste bin at home and wash your hands.

Adapted: HKL Counseling Checklist (Oct 2020) and Hosp Selayang Palliative Unit Information Leaflet (Administration of Transdermal Fentanyl Patch).

Appendix 7

GUIDE FOR NALOXONE USE

GENERAL PRINCIPLES:

- Naloxone, a specific opioid antagonist, is seldom necessary in the palliative care setting when opioids are appropriately titrated against the patient's pain.
- It is indicated for the reversal of opioid-induced respiratory depression and not for treating drowsiness and/or delirium associated with opioids.
- The dose administered should be carefully titrated against level of consciousness and satisfactory respiratory function (≥8 breaths/minute and no cyanosis).
- Titration is important to avoid acute withdrawal syndrome and severe pain.

PHARMACOKINETICS & AVAILABILITY:

- Route of administration: IV is preferable, but SC or IM can also be used
- Onset of action: 1 - 2 minutes (IV) and 2 - 5 minutes (SC/IM)
- Half-life: approximately 1 hour
- Pack size: 1 ampoule = 400 mcg/1 ml
- Adverse effects (usually with large bolus doses): abdominal cramps, nausea and vomiting, flushing, arrhythmias and erythema at injection site

TREATMENT:

- Respiratory depression is usually preceded by a progressive reduction in consciousness.
- If the respiratory rate ≥8 breaths/minute and patient can be easily aroused (e.g. opens eyes to verbal command), monitor patient closely and consider omitting or reducing the dose of the regular opioid.
- If respiratory rate is ≤8 breaths/min and patient is unresponsive, discontinue the ongoing opioid (e.g. stop CSCI/CIVI, remove TD patch) and naloxone should be administered.
    - Dilute 1 ampoule (400 mcg) of naloxone in 10 ml water for injection
    - Administer small boluses of 0.5 ml (20 mcg) every two minutes until respiratory rate is satisfactory, and patient is easily arousable (need not be fully alert)
    - After the last dose of naloxone, continue to monitor the patient
    - Further boluses of naloxone might be necessary because naloxone is shorter acting than the opioids.
    - A naloxone infusion may be considered if recovery is not satisfactory with multiple bolus doses.

- After patient recovers, the regular opioid regimen must be reviewed to consider possible causes for the respiratory depression (e.g. drug interactions, drug accumulation due to renal impairment, medication errors) and necessary modifications made to the regimen.

ADDITIONAL CAUTIONS:

- Do not use large bolus doses e.g. “1 ampoule stat” in patients who are receiving opioids for chronic pain relief.
- Pupil size is an unreliable indicator of opioid overdose in patients taking regular opioids
- Naloxone should not be given to patients on opioids when death is expected and imminent; a slow respiratory rate is a normal occurrence.

Source: Wilcock A. Howard P, Charlesworth S. Palliative Care Formulary. Eighth Edition. London: Pharmaceutical Press; 2022.

LIST OF ABBREVIATIONS

AEs	adverse effects
ATC	around-the-clock
AUC	area under the curve
BD	two times a day
BPI	Brief Pain Inventory
BQ-II	The Barriers Questionnaire II
CAM	complementary and alternative medicine
CGA	corrected gestational age
CI	confidence interval
CPG	Clinical Practice Guidelines
CPN	coeliac plexus neurolysis
CNS	central nervous system
COMM	Current Opioid Misuse Measure
COX-2	cyclooxygenase-2
CR	controlled-release
CrCL	Creatinine Clearance
CV	cardiovascular
DN4	Doeleur Neuropathique en 4
EBRT	external beam therapy
eGFR	estimated glomerular filtration rate
EPCRC	European Palliative Care Research Collaborative
ESAS	Edmonton Symptom Assessment System
ESAS-CS	Edmonton Symptom Assessment System with additional symptoms of constipation, sleep and added time window of “past 24 hours”
ESAS-r-CS	Edmonton Symptom Assessment System with a time window of “now”
FLACC	Face Legs Activity Cry Consolability
FPS	Faces Pain Scale
FST	fentanyl sublingual tablets
g	gramme
GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and Evaluation
Gy	Gray (unit of ionising radiation dose)
IASP	International Association for the Study of Pain
IPOS	Integrated Palliative Care Outcome Scale
IR	immediate release
IV	intravenous
kg	kilogramme
LANSS	The Leeds Assessment of Neuropathic Symptoms and Signs
max	maximum
mcg	microgramme
MD	mean difference
MEDD	morphine milligramme equivalent daily dose
mg	milligramme
min	minute
ml	milliliter
MPQ	McGill Pain Questionnaire
MSAS	Memorial Symptom Assessment Scale
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide

NCCN	National Comprehensive Cancer Network
NMDA	N-methyl-D-aspartate
NNH	number needed to harm
NNT	number needed to treat
NRS	Numeric Rating Scale
NRS-11	Numeric Rating Scale (0 - 10)
NSAIDs	nonsteroidal anti-inflammatory drugs
OD	daily
OMED	oral morphine equivalent daily dose
ONJ	osteonecrosis of the jaw
OR	odds ratio
ORT	Opioid Risk Tool
OTFC	oral transmucosal fentanyl citrate
PAINAD	Pain Assessment in Advanced Dementia tool
PFE	pain flare-effect
PO	by mouth
QoL	quality of life
RANK	receptor activator of nuclear factor kappa beta
RCT	randomised controlled trial
RD	risk difference
RR	risk ratio
SAEs	severe adverse events
SBRT	stereotactic body radiotherapy
SC	subcutaneous
SE	side effects
SHG	superior hypogastric plexus
SNRIs	selective norepinephrine reuptake inhibitors
SOAPP-R	Screener and Opioid Assessment for Patients with Pain-Revised
SR	sustained release
SRE	skeletal-related events
SMD	standardised mean difference
TD	transdermal
TDS	three times a day
TENS	Transcutaneous Electrical Nerve Stimulation
Tmax	time to peak drug concentration
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organisation
WMD	Weighted mean difference
153Sm	(153Sm) lexidronam
186Re	rhenium (186Re) obisbemeda
188Re	Rhenium-188
223Ra	Radium-223

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