SIGN

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Scottish Intercollegiate Guidelines Network

Control of Pain in Patients with Cancer

Developed in collaboration with the Scottish Cancer Therapy Network

A National Clinical Guideline

June 2000

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research[1] and are set out in the following tables.

STATEMENTS OF EVIDENCE

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

GRADES OF RECOMMENDATIONS

A **Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.**
(Evidence levels Ia, Ib)

B **Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.**
(Evidence levels IIa, IIb, III)

C **Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.**
(Evidence level IV)

GOOD PRACTICE POINTS

☑ Recommended best practice based on the clinical experience of the guideline development group.

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Notes for users of the guideline

DEVELOPMENT OF LOCAL GUIDELINES

It is intended that this guideline will be adopted after local discussion involving clinical staff and management. The Area Clinical Effectiveness Committee should be fully involved. Local arrangements may then be made for the derivation of specific local guidelines to implement the national guideline in individual hospitals, units and practices and for securing compliance with them. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

SIGN consents to the copying of this guideline for the purpose of producing local guidelines for use in Scotland. For details of how to order further copies of this or any other SIGN publication, see inside back cover.

STATEMENT OF INTENT

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve.

These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be fully documented in the patient's case notes at the time the relevant decision is taken.

A background paper on the legal implications of guidelines is available from the SIGN Secretariat.

REVIEW OF THE GUIDELINE

This guideline was issued in June 2000 and will be reviewed in 2002 or sooner if new evidence becomes available. Any amendments in the interim period will be noted on the SIGN website. Comments are invited to assist the review process. All correspondence and requests for further information regarding the guideline should be addressed to:

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Abbreviations

CNS	Clinical nurse specialists
COX-2	Cyclo-oxygenase-2
GI	Gastrointestinal
GP	General practitioner
LHRH	Luteinising hormone-releasing hormone
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drugs
PCA	Patient controlled analgesia
SCLC	Small cell lung cancer
SCTN	Scottish Cancer Therapy Network
SIGN	Scottish Intercollegiate Guidelines Network
SSRI	Selective serotonin reuptake inhibitors
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue score
VRS	Verbal rating scale
WHO	World Health Organisation

Summary of recommendations

ASSESSMENT OF PAIN IN PATIENTS WITH CANCER

B	Prior to treatment an accurate assessment should be performed to determine the type and severity of pain, and its effect on the patient.
B	The patient should be the prime assessor of his or her pain.
C	For effective pain control the physical, functional, psychosocial, and spiritual dimensions should be assessed.
B	The severity of pain and the overall distress caused to the patient should be differentiated and each treated appropriately.
B	A simple formal assessment tool should be used in the ongoing assessment of pain.
B	All health care professionals involved in cancer care should be educated and trained in assessing pain as well as in the principles of its control.
C	Sudden severe pain in patients with cancer should be recognised by all health professionals as a medical emergency and patients should be seen and assessed without delay.

PRINCIPLES OF MANAGEMENT OF PAIN IN PATIENTS WITH CANCER

A	Patients should be given information and instruction about pain and pain management and be encouraged to take an active role in their pain management.
B	The principles of treatment outlined in the WHO Cancer Pain Relief programme should be followed when treating pain in patients with cancer.
B	This treatment strategy should be the standard against which all other treatments for pain in patients with cancer are tested.
B	For appropriate use of the WHO analgesic ladder, analgesics should be selected depending upon initial assessment and the dose titrated as a result of ongoing regular reassessment of response.
B	A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain.
B	Prescribing of primary analgesia should always be adjusted as the pain severity alters.
B	If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency.
B	All patients with moderate to severe cancer pain, regardless of aetiology, should receive a trial of opioid analgesia.
B	Analgesia for continuous pain should be prescribed on a regular basis not 'as required'.

CHOICE OF ANALGESIA FOR CANCER PAIN

WHO ANALGESIC LADDER STEP 1: MILD PAIN

A Patients with mild pain should receive either a NSAID or paracetamol at licensed doses. The choice should be based on a risk/benefit analysis for each individual patient.

A Patients receiving a NSAID who are at risk of gastrointestinal side effects should be prescribed misoprostol 200 µg two or three times a day or omeprazole 20 mg once a day.

A Patients receiving a NSAID who develop gastrointestinal side effects but require to continue this therapy, should receive omeprazole 20mg daily.

WHO ANALGESIC LADDER STEP 2: MILD TO MODERATE PAIN

B Patients with mild to moderate pain should receive either codeine, dihydrocodeine or dextropropoxyphene plus paracetamol or an NSAID.

C If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, do not change to another opioid for mild to moderate pain. Move to step 3 of the analgesic ladder.

C Compound analgesics containing subtherapeutic doses of opioids for mild to moderate pain should not be used for pain control in patients with cancer.

WHO ANALGESIC LADDER STEP 3: MODERATE TO SEVERE PAIN

B Morphine or diamorphine should be used to treat moderate to severe pain in patients with cancer.

C The oral route is the recommended route of administration and should be used where possible.

B A trial of alternative opioids should be considered for moderate to severe pain where dose titration is limited by side effects of morphine/diamorphine.

USE OF OPIOIDS IN TREATMENT OF MODERATE TO SEVERE CANCER PAIN

INITIATING AND TITRATING ORAL MORPHINE

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

C Where possible, titration should be carried out with a normal release morphine preparation.

C Normal release morphine preparations must be given every four hours to maintain constant analgesic levels.

C When initiating normal release morphine, start with 5-10 mg orally at four hourly intervals, unless there are contraindications.

BREAKTHROUGH ANALGESIA

C Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of a normal release morphine.

C Breakthrough analgesia should be one sixth of the total regular daily dose of oral morphine.

C Breakthrough analgesia should be administered at any time outwith regular analgesia if the patient is in pain.

CONVERTING TO CONTROLLED RELEASE PREPARATIONS

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

B When transferring a patient from four hourly normal release morphine to a controlled release preparation start the controlled release preparation at the time the next normal release morphine formulation dose is due and discontinue the regular normal release morphine.

SIDE EFFECTS, TOXICITY, TOLERANCE AND DEPENDENCE

B Patients receiving an opioid must have access to regular prophylactic laxatives. A combination of stimulant and softening laxative will be required.

C Opioid toxicity should be managed by reducing the dose of opioid, ensuring adequate hydration and treating the agitation/confusion with haloperidol 1·5-3 mg orally or subcutaneously. This dose can be repeated hourly in the acute situation.

B Initiation of opioid analgesia should not be delayed by anxiety over pharmacological tolerance as in clinical practice this does not occur.

C Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence.

B Patients should be reassured that they will not become psychologically dependent on their opioid analgesia.

PARENTERAL ADMINISTRATION

B Patients requiring parenteral opioids should receive the appropriate dose of diamorphine via the subcutaneous route.

C To calculate the 24 hour dose of subcutaneous diamorphine divide the total 24 hour oral dose of morphine by three. Administer this dose of diamorphine subcutaneously over 24 hours.

C When converting from oral morphine to subcutaneous diamorphine, remember to prescribe a subcutaneous breakthrough dose which should be one sixth of the total daily dose of regular subcutaneous diamorphine.

C To calculate the 24 hour dose of oral morphine required, multiply the total daily dose of subcutaneous diamorphine being administered by two (if pain is stable) or three (if pain control is not satisfactory). If pain is stable, administer this as a controlled release preparation.

C Analgesia for breakthrough pain should be prescribed as a normal release oral morphine preparation at one sixth of the total daily dose of oral morphine.

C Advice on stability of commonly used drug combinations for continuous subcutaneous infusion should be available to staff who prepare these infusions.

C Advice on the use of other combinations should be taken from palliative care specialists.

C All staff using syringe drivers, including community based health care professionals, must be fully trained in their correct use.

C At the point of use, staff should have access to manufacturer's instructions for any infusion device used to deliver continuous subcutaneous infusions of opioids for moderate to severe pain.

C Safe systems for use and management of syringe drivers must be in place as detailed in guidance issued by the Scottish Executive Department of Health.

ALTERNATIVE OPIOIDS

B Alternative opioids can be tried in patients with opioid sensitive pain who are unable to tolerate morphine side effects

B Transdermal fentanyl is an effective analgesic for severe pain and can be used in patients with stable pain states as an alternative to morphine.

B Hydromorphone should be considered as a useful alternative in patients if morphine is causing cognitive impairment or where morphine is poorly tolerated.

B Oxycodone should be considered as an alternative in patients unable to tolerate morphine.

ADJUVANT ANALGESICS

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

C A therapeutic trial of oral high dose dexmethasone should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, spinal cord compression, or hepatic capsular pain (unless there are contraindications). In some clinical situations (e.g. if the patient is vomiting) it may be necessary to use the intravenous route.

A Mexiletine should not be used routinely as an adjuvant analgesic.

SYSTEMIC ANTI-CANCER THERAPY

A In patients with metastatic breast cancer who have progressive disease despite prior tamoxifen, the use of specific aromatase inhibitors such as anastrazole and letrazole should be considered.

C Primary endocrine therapy should be considered for all patients presenting with prostatic carcinoma and painful bone metastases.

C Maximum androgen blockade should be considered for patients with prostate cancer with worsening bone pain or progression on current single agent endocrine therapy.

RADIOTHERAPY

C Radiotherapy should be considered for painful bone metastases.

C The management of mechanical bone pain is more complex and if the patient is fit enough should involve consultation with an orthopaedic surgeon.

B Radioactive strontium should be considered for the management of pain due to widespread bone metastases from prostatic carcinoma.

C High dose steroids and radiotherapy should be considered for headache due to cerebral metastases. (The oral route is preferred, but intravenous administration may be necessary, e.g. if the patient is vomiting.)

BISPHOSPHONATES

A Bisphosphonate treatment should be considered for all patients with multiple myeloma.

A Bisphosphonates should be considered in the management of breast cancer patients who have pain due to metastatic bone disease.

INTERVENTIONAL TECHNIQUES FOR THE TREATMENT OF PAIN FROM CANCER

A In patients with upper abdominal pain, especially secondary to pancreatic cancer, coeliac plexus block should be considered.

C All professionals looking after patients with pain from cancer should be aware of the range of neurosurgical and anaesthetic techniques available for the relief of pain.

C All professionals looking after patients with pain from cancer should have access to a specialist pain relief service, able to offer the techniques described above.

C If a patient's pain is not controlled by other measures, then the advice of a specialist in pain relief should be sought, with a view to performing one of the above procedures.

EDUCATION ON PAIN MANAGEMENT IN CANCER PATIENTS

B Pre-registration curricula for health care professionals should place greater emphasis on pain management education.

B Continuing pain management education programmes should be available to all health care professionals caring for patients with cancer.

A All patients with cancer should have access to a health care professional appropriately qualified to offer advice and information, both verbal and written, regarding pain and effective pain management.

B Family members should be offered information and education regarding the principles of pain and its management in order to address their lack of knowledge and concerns regarding analgesic administration, tolerance and addiction.

PSYCHOSOCIAL ISSUES

B A thorough assessment of the patient's psychological and social state should be carried out. This should include assessment of anxiety and, in particular, depression, as well as the patient's beliefs about pain.

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

C Assessment should also be made of the patient's and family's beliefs about and responses to pain.

C Patients with cancer pain should be given an opportunity to be trained in some form of relaxation as an adjunct to pharmacological pain control.

1 Introduction

1.1 DEFINITIONS OF PAIN

Pain has been defined in many ways:

- *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*.[2]
- *"Pain is a category of complex experiences, not a single sensation produced by a single stimulus"*.[3]
- *"Pain is what the experiencing person says it is, existing whenever he says it does"*.[4]

For the purposes of this guideline, the first of these definitions is used. Pain is a subjective phenomenon. It is a sensation in part of the body, always unpleasant, and also has an emotional component.

A study analysing data from 11 randomised double-blind trials found that mild pain corresponds to a score of less than 30 mm on a visual analogue scale ranging from 0 mm (= no pain) to 100 mm (= worst possible pain), moderate pain 31-54 mm and severe pain above 55 mm.[5] The American Pain Society[6] and the US Agency for Health Care Policy and Research[7] analysed studies relating pain to daily functioning and found that pain scores higher than 50 (moderate to severe pain) interfered with function.[8, 9]

1.2 BACKGROUND

Many patients think cancer and pain are synonymous, but the reality is more complex:

- One third of patients with cancer do not experience *severe* pain.
- Of the two-thirds of cancer patients who *do* experience *severe* pain, around 88% can and should have their pain adequately controlled by the application of basic principles of pain management.[10]
- Of those cancer patients who have pain, 80% have more than two pains[11] and 40% have pain before the terminal phase of their illness.[8]

Accurate assessment of *each* pain is vital as some pains in patients with advancing cancer are due to non-malignant causes and different types of pain are treated differently. It is important to remember that co-morbidity and treatment side effects can be responsible for pain.[12] The patient's perception of the pain and the extent of the associated problems must be carefully assessed. Patients with long term pain problems which are not adequately controlled and associated with advancing cancer, suffer both physically and mentally.

To facilitate optimal pain management a multidisciplinary approach is essential. Each patient will have different requirements but all professionals involved in the management of patients with cancer pain should be aware of the potential benefits of referring to other relevant disciplines. Working in collaboration with the general practitioner (GP), specialists who may be able to assist with patients who have difficult pain problems include palliative care physicians, clinical nurse specialists (CNS), pain relief anaesthetists, pharmacists, psychologists, occupational therapists and physiotherapists.

1.3 THE NEED FOR A GUIDELINE

There are three main reasons for producing this guideline.

(1) The prevalence of (any) pain in patients with cancer is around 80% (range 52-82%).[13-17]

(2) There is evidence of poor pain control in around one third of patients in generalist settings whereas in specialist units only 5-10% of patients pain proves difficult to control (range 14-47%).[16, 17, 18]

(3) Current guidelines[19, 20, 21] are either not evidence-based, require updating, or there is no sense of local ownership. An exception to this is the Scottish Partnership Agency handbook on the role of drug therapy in the relief of pain and related symptoms, which has recently been updated with reference to current evidence and is a useful companion document to this guideline.[22]

1.4 DEVELOPMENT OF THE GUIDELINE

This guideline for the treatment of pain in patients with cancer was developed by the Scottish Cancer Therapy Network (SCTN) Palliative Care Focus Group. The remit of this multidisciplinary group covers all cancer types as, in general, symptoms found in different cancers are similar. The guideline is intended for use in patients aged 12 years and over: the management of younger children is outwith the scope of the guideline.

The guideline is based on a systematic and critical review of the literature. The level of evidence for some areas of the guideline and recommendations is low, reflecting the difficulty in performing randomised controlled trials in the area covered by the guideline. Details of the literature search undertaken for this guideline are provided at Annex 1. Recommendations for further research are at Annex 2. A minimum core data set to facilitate prospective audit of the guideline is included as Annex 3.

1.5 GOOD PRACTICE IN EFFECTIVE PAIN MANAGEMENT

In treating pain in patients with cancer the following should always be remembered:

- The patients' wishes and goals must be determined and the team treating the patient should centre on these. In many cases the patient may need help to appreciate what is actually achievable. Realistic hopes should be fostered.
- Optimum pain management may require multiprofessional input. To understand and effectively manage the pain suffered by patients with cancer requires a range of skills. Within the team, individuals with a diversity of training, but with a common purpose and goal may best meet these patients' needs.[23]
- With this team approach the patient should be aware of who is in overall control of their symptom management.
- Timely and open communication between team members is paramount.
- Professionals should recognise when pain is not controlled and make appropriate referral for a second opinion. This should occur earlier rather than later.
- Patients should be aware of their right to a second opinion.
- Patients should have ready access to a specialist in pain relief/palliative medicine physician, a CNS, and/or a pain relief anaesthetist, depending on their clinical requirements.

It is hoped that the development of Managed Clinical Networks in palliative care will facilitate the implementation of these principles into practice.

2 Education on pain management in cancer patients

2.1 EDUCATION AND HEALTH CARE PROFESSIONALS

Education of health care professionals has been shown to lead to improved control of pain in patients with cancer, but a large gap still exists between possible and actual pain control.[24]

Evidence level Ib

Barriers which have been proposed to explain inadequate pain management include lack of education of health care professionals regarding the mechanisms of pain, pain assessment and pain management; and inadequate knowledge and inappropriate attitudes amongst health care professionals, patients with cancer and lay carers.[24, 25, 26]

Evidence levels Ib and III

Pain management education is deficient in health care professionals' training.[25, 26] Studies have indicated educational programmes and in-depth training of health care professionals can positively impact on these professionals' knowledge and attitudes.[26, 27]

Evidence level IIb

B **Pre-registration curricula for health care professionals should place greater emphasis on pain management education.**

B **Continuing pain management education programmes should be available to all health care professionals caring for patients with cancer.**

Traditional methods of pain management education, i.e. lectures and case discussion, have not proven fully effective and alternative approaches need to be considered if pain management behaviour is to be altered significantly. The alternative approaches suggested included the publication, dissemination and implementation of pain management guidelines, wider use of pain assessment tools, public education and formulary restrictions.[28]

Evidence level III

Further research is needed to evaluate the impact of pain management education programmes for health care professionals on clinical practice and patient outcomes.

Increasing use of technology to manage the pain of patients with cancer in the community setting has resulted in an increased need for educational programmes aimed at community-based health care professionals *(see section 7.8.4)*.

2.2 EDUCATION AND PATIENTS

There is an expectation by some professionals and lay persons that cancer inevitably means pain, and that little can be done to manage this pain. This, as well as misconceptions and fears regarding the use of morphine *(see section 7.7)*, reduces the probability of effective pain management being achieved.

Pain education programmes that include guidance by an appropriately qualified health care professional and use of verbal and written material have been shown to improve significantly patients' knowledge of pain, decrease their pain intensity and reduce concerns regarding tolerance and addiction.[29, 30, 31]

Evidence levels Ib and III

A **All patients with cancer should have access to a health care professional appropriately qualified to offer advice and information, both verbal and written, regarding pain and effective pain management.**

Increased availability and accessibility of information on the internet, heightened public awareness of patients' rights, and shorter hospital admissions impact on the educational needs of patients with cancer and pain.[32] Explanatory leaflets in the appropriate language should be readily available and the use of multimedia and information technology should be considered when planning future pain education programmes for patients and health care professionals.[33]

Evidence levels Ib and IV

Information for health professionals on specialist palliative care services and pain clinics is detailed in Annex 4. Details of recognised support groups, telephone helplines and written information for patients are given in Annex 5.

2.3 EDUCATION AND FAMILY

Family members are increasingly involved in the management of cancer related pain for patients cared for at home. Research has shown that family members demonstrate areas of lack of knowledge of pain or hold attitudes to pain and its management which may impact negatively on patients' pain outcome.[34] Pain education programmes that involve patients and their carers significantly affect the patient's pain experience.[35]

Evidence level III

B **Family members should be offered information and education regarding the principles of pain and its management in order to address their lack of knowledge and concerns regarding analgesic administration, tolerance and addiction.**

3 Assessment of pain in patients with cancer

3.1 WHY ASSESS PAIN?

Effective control of pain in patients with cancer requires an accurate assessment.[36] Accurate assessment and diagnosis of the type of pain, its severity, and its effect on the person are necessary to plan appropriate interventions or treatments, and are an integral part of overall clinical assessment.[37-42] The aetiology of the pain should also be considered: 5-10% of patients with malignant disease report pain due to conditions other than the cancer.[43]

Evidence levels III and IV

B **Prior to treatment an accurate assessment should be performed to determine the type and severity of pain, and its effect on the patient.**

3.2 WHO SHOULD ASSESS PAIN?

Health professionals have been shown to underestimate the level of pain a patient is experiencing, and this discrepancy between estimations widens as the pain increases in severity.[44, 45] Family members, however, tend to overestimate pain in their relatives.[46] The patient, if competent and able to communicate, is the most reliable assessor of pain and should, where possible, be the prime assessor of his or her pain.[8]

Evidence level III

B **The patient should be the prime assessor of his or her pain.**

Involving the patient closely in the assessment and goal setting will encourage the development of trust and enhance the probability of successful pain control. In patients with communication difficulties, such as those suffering from delirium, dementia, or dysphasia, careful consideration should be given to assessment by lay carers.

In tandem with the patient's assessment, members of the multidisciplinary team, principally doctors and nurses, should contribute to the overall assessment. Others, such as psychologists, physiotherapists, pharmacists and occupational therapists, will contribute as they become involved in the management of the patient. The complexity of the patient's pain and concomitant medical factors will influence how many professionals might be involved in the pain management. Good communication will be vital.

3.3 WHAT TO ASSESS?

Pain is more than a physical phenomenon.[47] Despite this, the psychological, social and spiritual aspects of pain are not always considered. Comprehensive assessment of pain, requires consideration of the following domains:

Evidence level IV

(1) **Physical effects / manifestations of pain**[12]

(2) **Functional effects**
- interference with activities of daily living.[9]

(3) **Psychosocial factors**[36, 48]
- level of anxiety, mood, cultural influences, fears, effects on inter-personal relationships, factors affecting pain thresholds *(see Table 1)*.

Evidence level III

(4) **Spiritual aspects**

Spirituality relates to ideas of meaning of purpose and of the continuity of life. It does not always include a religious component.[49, 50] Meaningful spiritual assessment comes from understanding that there can be no one clear definition of 'spiritual needs'. It requires a 'person centred approach', focused on the individual.[51] Spiritual pain is a result of the experience of illness which may threaten an individual with spiritual disintegration, isolation and loss of meaning.

Spiritual assessment suffers from the misconception that spiritual equals religious. Atheists may have spiritual needs. Chaplains and members of the multidisciplinary team are experienced in meeting spiritual needs, and can assist the individual's search for meaning from different faith perspectives, or from none.

The meaning of suffering may well be equated with spiritual pain/spiritual anguish. It has been stated that suffering can include physical pain but is by no means limited to it.[52] There is no doubt that for some suffering can have a meaning, to others it is senseless and then often unbearable. The fact that 'suffering' can exacerbate physical pain is well described by Rene Leriche who some 60 years ago wrote *'Pain is the resultant of the conflict between a stimulus and the whole individual'*.[53] *Evidence level IV*

Kaye (1990) details a wide variety of emotions displayed in spiritual pain and has categorised them in terms of:[54]

- the past *(painful memories, regret, failure, guilt)*
- the present *(isolation, unfairness, anger)*
- the future *(fear, hopelessness)*.

C **For effective pain control the physical, functional, psychosocial, and spiritual dimensions should be assessed.**

☑ Health care professionals should know how to contact their chaplain or spiritual representative relevant to the patient's faith and beliefs and should be aware when input is required.

Table 1

FACTORS AFFECTING PAIN TOLERANCE *(adapted from Twycross and Lack*[11]*)*

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

3.4 PAIN TOLERANCE

Pain tolerance varies considerably between patients. What is bearable to one individual may be insufferable to another[48] and failure to differentiate between the severity of the pain and the distress caused to the patient may lead to over-sedation of the patient.

Evidence level III

B **The severity of pain and the overall distress caused to the patient should be differentiated and each treated appropriately.**

Pain tolerance is influenced by a variety of factors[55] *(see Table 1, adapted from Twycross and Lack*[11]).

3.5 HOW TO ASSESS PAIN

Diagnosis of the cause of pain and the functional and psychosocial impact[42] is achieved by a full assessment (history, physical examination, investigations, standardised assessment tools).

Evidence level III

3.5.1 HISTORY

Detailed history taking is vital to comprehensive assessment. Listen to the patient carefully and determine:

- Site and number of pains
- Intensity/severity of pains
- Radiation of pain
- Timing of pain
- Quality of pain
- Aggravating and relieving factors
- Aetiology of pain
  - pain caused by cancer
  - pain caused by treatment
  - pain associated with cancer related debility (e.g. decubitus ulcers)
  - pain unrelated to cancer or treatment
- Type of pain
  - somatic
  - visceral
  - neuropathic
  - sympathetically mediated
  - mixed
  - anguish
- Analgesic drug history
- Presence of clinically significant psychological disorder e.g. anxiety and/or depression.

3.5.2 PHYSICAL EXAMINATION

Ideally a full physical examination should be undertaken, aimed at reaching a diagnosis and establishing best effective treatment. If the patient is very weak, an examination targeted to the area of pain may be sufficient.

3.5.3 INVESTIGATIONS

Investigations should be restricted to those that are likely to give results which will affect management. This is especially so in those patients considered near the end of life, when many routine or screening investigations may cause unnecessary disturbance. In such patients only relevant investigations that will significantly influence the management should be performed.

☑ In patients nearing the end of life, investigations should be limited to those that will affect management of their symptoms.

Table 2

PAIN ASSESSMENT TOOLS AND THEIR APPLICATION

Tool	***Description / Setting***	
Memorial Pain Assessment Card[56]	A simple, rapidly completed questionnaire which measures intensity, relief of pain, and psychological distress. Developed for use in hospitals.	
Wisconsin Brief Pain Inventory[8, 57]	Widely used across cultures to assess pain. Measures intensity and relief of pain, psychological distress, and functional impairment. A valid and reliably tested tool used in research studies. A shorterned version has been used in research and in the hospice setting.	*Evidence level III*
McGill Pain Questionnaire[58]	One of the first pain assessment tools, which revolutionised assessment. The full chart is very detailed and time consuming to complete, but a shortened version is available. Used in research.	
McGill Home Recording Chart	Developed for use at home.	
Simpler measures of pain intensity:		
Numerical Rating Scale (NRS)	The patient rates pain on a scale from 0 to 10.	
Visual Analogue Score (VAS)	The patient indicates intensity of pain on a 10 cm line marked from "no pain" at one end to "severe pain" at the other end.[5]	*Evidence level III*
Likkert or Verbal Rating Scale (VRS)[9]	The patient rates the pain verbally, e.g. "none", "mild", "moderate" or "severe."	
Western General Hospital, Edinburgh Observation Chart	Under development in hospital setting.	

3.5.4 STANDARDISED ASSESSMENT TOOLS

Because pain has so many confounding factors, a logical approach and the use of validated tools may help to clarify the different aspects of a patient's pain. Body charts in particular, or even simple sketches giving a graphical description of pain, can be useful for reference purposes when pain is being assessed, especially when different members of the multidisciplinary team are involved.

Pain assessment tools must measure:

- intensity of pain
- relief of pain
- psychological distress
- functional impairment.

A summary of the available assessment tools and their application and validation is provided in Table 2. A number of these and a wide range of other pain and quality of life assessment tools are available on the Internet at www.qlmed.org.

Assessment tools and charts are not routinely used and their use should be encouraged in all settings.[59, 60, 61] *Evidence level IV*

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

☑ The guideline development group recommends use of a Likkert Scale for pain assessment and this is included in the minimum data set in Annex 3. However, it is recognised that some combination of numerical, verbal, and visual analogue scales may be needed, depending on the individual patient.

3.6 WHEN TO ASSESS?

3.6.1 COMMUNITY

In most cases the GP is the first point of contact when patients present with symptoms suggestive of malignancy. Pain may be the presenting symptom and an initial full assessment and initiation of treatment of the pain should be made at such contact.

☑ The importance of regularly assessing pain and the effect of analgesics on the pain cannot be over emphasised.

The timing of reassessment will depend on individual circumstances. If pain is difficult to control then asking the patient at home to assess regularly the severity of their own pain four times a day using a simple method will be beneficial.

A sudden exacerbation of pain may require an urgent home visit. The frequency of visiting thereafter will depend on the response to treatment and the management plan agreed between the patient, carer, nurse, and the GP.[62] *Evidence level IV*

C **Sudden severe pain in patients with cancer should be recognised by all health professionals as a medical emergency and patients should be seen and assessed without delay.**

Problems of continuity of care and lack of communication have been reported with the advent of out of hours GP emergency cover and deputising services.[63]

Evidence level IV

☑ Procedures for rapid assessment and management of pain in patients with cancer should be agreed by co-operating general practitioners and information given to patients of on call arrangements.

3.6.2 ACUTE HOSPITAL SETTING

In the acute hospital setting an initial pain assessment should be performed and charted:

- on admission if the patient complains of pain
- on admission if the patient is already taking large doses of analgesics
- before initiating a new therapeutic protocol.

Thereafter, regular recording of the patient's verbal pain score can help health professionals to understand the severity of patient's pain and to monitor the response to analgesics.[64] Regular assessment of pain remains vital, and the exact frequency will be dependent on the severity of the pain and the distress of the patient.

Evidence level III

3.7 BARRIERS TO PAIN ASSESSMENT

For pain to be accurately assessed and thereby appropriately managed, health professionals must be aware of the barriers to and the complexities of pain assessment. These include:[44, 60, 65-67]

- The multidimensional, subjective nature of pain
- Lack of clearly defined language of pain
- Anxiety or depression
- Poor communication between patient and health care professional:
  - under-reporting by patient
  - under-assessing by health professionals/carers
  - language/ethnicity[68]
  - impaired hearing
  - reduced cognitive ability
  - reduced level of consciousness
  - incorrect attitude and knowledge deficit in health professionals regarding adequate pain control.

Evidence levels III and IV

Educational needs assessments in primary care have shown that most GPs and community nurses recognise the deficiencies in their education and training and are keen to enhance their knowledge, skills and attitudes with regard to pain and symptom control.[69-72]

Evidence level III

B **All health care professionals involved in cancer care should be educated and trained in assessing pain as well as in the principles of its control.**

4 Psychosocial issues

4.1 ASSESSMENT OF PSYCHOSOCIAL ASPECTS

The experience of pain is a highly complex phenomenon with physical, behavioural, cognitive, emotional, spiritual, and interpersonal aspects. This multidimensional nature of pain must be acknowledged in the assessment and management of patients.[73]

Evidence level IV

Patients' beliefs about cancer pain and their behaviours in response to it often lead to pain remaining unrelieved. Similarly, aspects of doctors' and nurses' beliefs and behaviours can have the same effect.[74] Pain in patients with cancer is affected by psychological processes including emotions, cognition, and motivation as well as by situational factors,[55] all of which can also be influenced by cultural, ethnic, and linguistic factors.[36]

In more specific terms, mood disturbance and beliefs about the meaning of pain can affect perceived pain intensity.[75] Patients with cancer have more intense emotional reactions to pain, including anxiety, depression, bodily preoccupation, hypochondriasis and neuroticism, than patients with non-malignant pain. This may be because the effects of the chronic pain are added to the effects of the cancer itself.[76] Many patients with cancer pain feel hopeless and despairing and can find no meaning in their pain at all.[76] There is also evidence that pain and psychiatric morbidity among cancer patients are highly correlated.[77]

Evidence levels III and IV

4.2 DIAGNOSIS OF PAIN AND DEPRESSION

The prevalence of depressive disorders of all types has been found to be significantly higher in patients with cancer who have high pain scores than in patients with low pain scores, even when patients with high pain scores have a significantly lower previous history of depression. There is therefore some suggestion that not only are pain and psychiatric morbidity correlated but that cancer pain may play a role in producing or exacerbating depression.[77] Depression is often missed in cancer patients.[78] There is an overlap between symptoms of depression, symptoms of cancer, and the effects of cancer treatment. However, it has been found that careful and extensive questioning can elucidate the extent to which the symptom relates to emotional distress, to the cancer, or to the treatment.[77]

Evidence levels III and IV

B **A thorough assessment of the patient's psychological and social state should be carried out. This should include assessment of anxiety and, in particular, depression, as well as the patient's beliefs about pain.**

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

☑ Patients who are in pain and depressed should have their pain and depression treated.

Family stress and distress is a frequent consequence of pain in a patient with cancer, and both the patient and the family can have a reciprocally deleterious effect on each other.[76] Also as the patient's weakness, debility, and adverse emotional reactions are exacerbated by uncontrolled pain, the patient consequently may lose contact with friends and curtail social activities.[76]

Evidence level IV

C **Assessment should also be made of the patient's and family's beliefs about and responses to pain.**

Further research is needed to establish whether reducing pain decreases depression and to determine when the depression should be treated directly.[77, 79]

4.3 PSYCHOSOCIAL INTERVENTIONS IN PATIENTS WITH CANCER

A meta-analysis of psychoeducational care of patients with cancer concluded that psychoeducational care was beneficial to adults with cancer in relation to anxiety, depression, mood, nausea, vomiting, pain and knowledge.[80] Differentiating among the effects of the various types of psychoeducational care in this analysis was problematic for most of the outcomes, although the effect of relaxation type interventions was beneficial in patients with cancer pain. However, the number of patients in each of the five studies included was not documented and all studies were conducted on patients in the United States and the results are not necessarily generalisable to patients in the UK.

A second meta-analysis on the effects of non-pharmacological interventions such as relaxation, imagery, information provision, and music on pain in patients with cancer produced inconclusive results.[81] Further research and evaluation is required.

Results from a meta-analysis of different psychosocial interventions indicate that these types of intervention have a positive effect on emotional and functional adjustment of cancer patients. The studies analysed included predominately white females from the United States and again may not be generalisable to patients in the UK or males.[82]

There is some evidence from small randomised controlled trials that relaxation therapy is beneficial in reducing cancer treatment-related pain.[83] There are few well designed RCTs with large enough sample sizes to demonstrate an effect using relaxation as an adjunct to pharmacological pain control in patients with cancer pain.[84, 85, 86]

Evidence levels Ib, IIa and IV

Although some studies demonstrate the effectiveness of hypnosis in patients with cancer[30, 87] there is little evidence for the specific effect of hypnosis in the relief of pain in patients with cancer. One study concluded that hypnosis was effective in reducing oral pain for patients undergoing marrow transplantation but that a cognitive-behavioural intervention was not effective.[83] A further study found that patients who received either relaxation or were trained in cognitive behavioural skills reported less pain than controls.[88] However, the hypothesis that training in cognitive behavioural skills would have an additive effect beyond that of relaxation was not confirmed.

Evidence level Ib

C **Patients with cancer pain should be given an opportunity to be trained in some form of relaxation as an adjunct to pharmacological pain control.**

☑ The form of relaxation should be tailored to the individual patient.

5 Principles of management of pain in patients with cancer

5.1 INTRODUCTION

The recommendations for drug therapy in this guideline are based largely on the systematic review on pain control carried out for the NHS National Cancer Research and Development Programme.[89] Many of the studies covered by the review are on non-malignant pain groups and single dose analgesic studies but because of similar mechanisms involved in pain sensation the findings can be extrapolated to the treatment of pain in patients with cancer.

All medical professionals have a responsibility to initiate immediate and short term pain relieving measures while considering options such as surgery, chemotherapy or radiotherapy.

Involvement of patients in their treatment improves pain control. A study of the effectiveness of a pain management intervention with patients with chronic cancer pain demonstrated that giving cancer patients an active role in their pain management had a beneficial effect on patients' pain experience.[31] Information and an explanation about their medication will form part of this.

Evidence level Ib

A **Patients should be given information and instruction about pain and pain management and be encouraged to take an active role in their pain management.**

5.2 WHO ANALGESIC LADDER

The general treatment strategy for cancer pain developed by the World Health Organisation (WHO) programme for cancer pain relief is illustrated in figure 1.[19]

The recommendations for each step of the analgesic ladder have not been individually evaluated in randomised controlled clinical trials. However using this treatment strategy up to 88% of patients obtain satisfactory relief from pain.[10, 90] Moreover it is established as effective in clinical practice.

Evidence level III

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

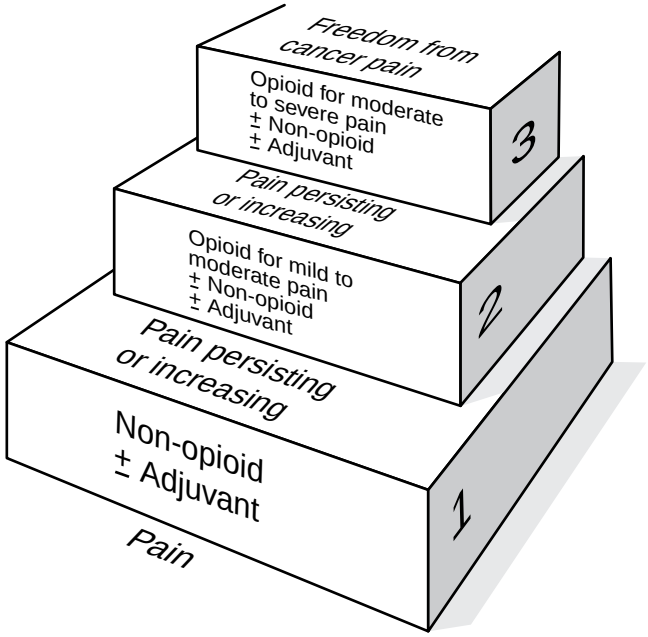
B **This treatment strategy should be the standard against which all other treatments for pain in patients with cancer are tested.**

5.3 OTHER MODES OF PAIN CONTROL

The WHO analgesic ladder is a statement of principles which can be used with a varying degree of interpretation, rather than a rigid framework. This method was never intended to be used in isolation and may have to be combined with other treatment modalities.

Figure 1

WHO ANALGESIC LADDER



(Reproduced by permission of the World Health Organisation)

For some pains, particularly short lived, fluctuating pain other strategies may need to be used. These may include the use of transcutaneous electrical nerve stimulation (TENS), acupuncture, nerve blocks and Entonox. TENS may be useful in chronic cancer pain, but there is no clear evidence of benefit.[89, 91]

Evidence level Ia

In many cases a multidisciplinary approach is required to give the optimum outcome for the patient. Health professionals involved may include anaesthetists, surgeons, physiotherapists, occupational therapists, oncologists, nurses, pharmacists, clinical psychologists and palliative care specialists.

☑ Optimum management of pain in patients with cancer requires a multidisciplinary approach.

5.4 USE OF THE WHO ANALGESIC LADDER

A basic prerequisite of any approach to pain relief is a complete patient assessment, including differentiating pain distress from pain severity *(see section 3.4)*. Choice of therapy is directed by the severity, the type and cause of the pain. The severity of pain determines the strength of analgesic required and the type and cause of the pain will influence the choice of adjuvant analgesic (any drug that has a primary indication other than for pain management, but is analgesic in some painful conditions). Type, cause and severity can only be determined from a thorough patient assessment.[10, 90] Effective use of the WHO ladder therefore depends on accurate regular pain assessment.

Evidence level III

B **For appropriate use of the WHO analgesic ladder, analgesics should be selected depending upon initial assessment and the dose titrated as a result of ongoing regular reassessment of response.**

5.4.1 SEVERITY OF PAIN

Paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), opioids for moderate pain, and opioids for severe pain form the basis of the WHO three-step ladder. Treatment should be adjusted from one step to the next according to increasing or decreasing pain severity, history of analgesic response, and side effect profile.

The extent to which pain responds to opioid analgesics varies depending on both patient and pain characteristics. No pain is predictably unresponsive to opioids. Neuropathic pain can respond to opioids, although the response may be incomplete.[92,93] All patients with moderate to severe cancer pain should have a trial of opioid analgesia.

Evidence level Ib

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

B **Prescribing of primary analgesia should always be adjusted as the pain severity alters.**

B **If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency.**

B **All patients with moderate to severe cancer pain, regardless of aetiology, should receive a trial of opioid analgesia.**

Chronic pain in patients with cancer is usually continuous and where this is so, therapeutic plasma levels of analgesics must be maintained. This can only be achieved when the drug is given regularly at correct intervals according to the pharmacokinetic and pharmacodynamic profile of the drug.[10, 90]

Evidence level III

B **Analgesia for continuous pain should be prescribed on a regular basis not 'as required'.**

It should be explained to the patient with chronic cancer pain that pain control medication must be taken regularly to gain optimal results *(see Annex 6 for key messages for patients from this guideline)*.

5.4.2 CAUSE AND TYPE OF PAIN

The cause and type of pain indicates which adjuvant analgesic should be used[10, 90] *(see section 8 and Annex 7).*

Evidence level III

5.5 TREATMENT-RELATED PAIN

Patients who have had treatment for their cancer may present with pain related to this treatment.[11] Surgery is the most common cause of these problems as it is inevitable that nerves and other tissue will be damaged by some operations, however meticulous the technique. This may cause diverse syndromes, the incidence of which is hard to estimate due to the lack of research in this area.[94] The advice of a pain specialist should be sought as soon as possible as these types of pain are difficult to treat.

Evidence levels Ia and IV

- ☑ When treatment-related pain is present, there should be early referral to a pain specialist.
- ☑ It is important that the possibility of pain caused by treatment is borne in mind and discussed with the patient, if possible, before treatment. Patients should be pre-warned that a consequence of treatment may be ongoing chronic pain.

6 Choice of analgesia for cancer pain

6.1 WHO ANALGESIC LADDER STEP 1

MILD PAIN

Drug options:	*paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)*

In multiple dose studies there is no comparative evidence for the superiority of paracetamol, aspirin or NSAIDs. In single dose studies of postoperative pain, NSAIDs are more effective than paracetamol, although paracetamol is also effective.[89]

Evidence level Ia

Given the different mechanisms of action, combining a NSAID with paracetamol may achieve improved analgesia but there is no trial evidence to support this theory.

The choice of non-opioid must depend on the individual risk/benefit balance for each patient. The side effect profile of each option is quite different:

Paracetamol has minimal toxicity at recommended doses[95] but at higher doses can cause fatal hepatotoxicity and renal damage.

Aspirin may be difficult to tolerate at analgesic doses due the wide range of side effects.[96]

Evidence level IV

NSAIDs have a significant incidence of serious and potentially fatal problems. The incidence of death from gastric bleeding following at least two months exposure to oral NSAID is estimated to be 1 in 1,200[89] whilst the incidence of renal dysfunction is not known. However those with existing renal disease[97, 98] cardiac failure, hepatic impairment and the elderly appear to be at higher risk of renal damage.[99] Vigilance is required to detect if patients are developing either of these problems. NSAIDs frequently cause fluid retention and may cause a rise in blood pressure,[100] which may be detrimental in some groups of patients.

NSAIDs show a direct dose response relationship in terms of desired effects and both gastrointestinal and renal adverse effects.[101, 102, 103] Limit on the maximum dose is dictated by an increase in side effects. Over this level little extra benefit is achieved for a large increase in the risk of side effects.[104]

Evidence levels Ia, III, and IV

A **Patients with mild pain should receive either a NSAID or paracetamol at licensed doses. The choice should be based on a risk/benefit analysis for each individual patient.**

Some patients are more at risk of serious gastrointestinal side effects from NSAIDs than others.[101] Groups shown to be at high risk are the elderly (>60 years old), smokers, those with a previous history of peptic ulcer, and those also receiving oral steroids or anticoagulants, and those with existing renal disease, cardiac failure or hepatic impairment.

Evidence level III

Misoprostol has been proven to reduce the risk of both gastric and duodenal ulcerations developing in patients taking NSAIDs[105] and is superior to both ranitidine[106] and sucralfate.[107] Lower doses of misoprostol (200 µg twice or three times a day) significantly reduce the incidence of NSAIDs-induced damage whilst having a lower incidence of side effects compared with 200 µg four times a day.[108]

Omeprazole is also effective at a dose of 20 mg daily in reducing the risk of gastric and duodenal erosions.[109, 110, 111] No trials published to date have compared misoprostol to omeprazole for prevention of NSAID induced gastrointestinal (GI) damage. However, omeprazole is significantly more effective than misoprostol in treating gastric or duodenal erosions in patients who have developed these and who require to continue taking a NSAIDs.[112, 113] A dose of 20 mg omeprazole daily was as effective as 40 mg daily.[113]

Evidence level Ib

The recent introduction of NSAIDs that selectively inhibit the isoenzyme cyclo-oxygenase-2 (COX-2) may offer a reduced risk of gastrointestinal damage.[114, 115] Whilst there is clear evidence that the more selective COX-2 inhibitors such as rofecoxib do produce fewer serious GI adverse reactions in average risk patients in short term studies,[114, 115] there is little published data on whether this benefit extends to high risk groups or in chronic use. For less selective agents such as meloxicam it is not yet clear whether the incidence of serious GI adverse effects is reduced at all therapeutic doses.[116, 117] The impact on non-GI side effects are unclear and there are remaining questions about their use in patients with previous history of GI ulceration and patients with vascular disease.[100]

Evidence levels Ia and IV

A **Patients receiving a NSAID who are at risk of gastrointestinal side effects* should be prescribed misoprostol 200 µg two or three times a day or omeprazole 20 mg once a day.**

A **Patients receiving a NSAID who develop gastrointestinal side effects but require to continue this therapy, should receive omeprazole 20 mg daily.**

* *>60 years old, smokers, previous history of peptic ulcer, concomitant use of oral steroids or anticoagulants, renal or hepatic disease and those with cardiac failure.*

6.2 WHO ANALGESIC LADDER STEP 2

MILD TO MODERATE PAIN

Drug options: *codeine, dihydrocodeine, dextropropoxyphene + step 1 non-opioids*

In single dose studies of mild to moderate postoperative pain NSAIDs are more effective at treating pain than opioids alone or in combination with paracetamol or aspirin. Paracetamol in combination with an opioid for mild to moderate pain is effective and appears to be marginally more effective than paracetamol alone.[89]

Evidence level Ia

While the efficacy achieved by single doses of oral opioids such as codeine is poor, multiple doses may perform better. There is logic in adding an opioid to paracetamol (e.g. cocodamol forte, coproxamol) or a NSAID or in adding an opioid to paracetamol plus a NSAID. This may reduce the dose of opioid required.[118]

Evidence level III

At therapeutic doses there is no evidence of superiority of one opioid for mild to moderate pain over another. In clinical practice it appears that codeine and dihydrocodeine are equipotent.[119, 120, 121, 122]

Evidence level IV

Tramadol is an opioid with additional effects on the monaminergic system.[123] At therapeutic doses its analgesic effect is similar to that of an opioid for mild to moderate pain in combination with a non-opioid.[89] The extent to which the dose can be titrated is limited as at doses just above the normal therapeutic dose tramadol can cause convulsions.[123] Tramadol also produces serious psychiatric reactions at therapeutic doses in some patients.[124] For these reasons it appears to offer little over existing opioids for mild to moderate pain in patients with cancer.

Evidence levels Ia, III and IV

B **Patients with mild to moderate pain should receive codeine, dihydrocodeine or dextropropoxyphene plus paracetamol or a NSAID.**

C **If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, do not change to another opioid for mild to moderate pain. Move to step 3 of the analgesic ladder.**

Codeine demonstrates a dose response curve to pain relief.[125, 126] There is evidence that combinations of codeine 60 mg and paracetamol 600-1000 mg are more effective than paracetamol alone at doses of 500-1500 mg. No evidence was found in clinical trials or meta-analysis to support the superiority of cocodamol 8/500 over paracetamol alone.[127]

Evidence levels Ia and Ib

Many compound preparations containing codeine and dihydrocodeine have apparent sub-therapeutic doses (less than 30 mg) of these opioids and therefore are not recommended for the management of chronic pain in patients with cancer *(see Annex 8)*.

C **Compound analgesics containing subtherapeutic doses of opioids for mild to moderate pain should not be used for pain control in patients with cancer.**

6.3 WHO ANALGESIC LADDER STEP 3

MODERATE TO SEVERE PAIN

Drug options:	*First line – morphine, diamorphine + step 1 non-opioids* *Alternative – fentanyl, hydromorphone, methadone, oxycodone, phenazocine, + step 1 non-opioids*

The opioid of choice for oral use is morphine.[128] The majority of patients tolerate oral morphine well and, due to the likelihood that patients will require to use medication chronically, the oral route is preferable to parenteral or rectal administration. Pain response is variable, but with dose titration a suitable level of analgesia can usually be achieved. The efficacy and safety of morphine is well established in clinical practice[10, 90] and the wide variety of morphine formulations available in the United Kingdom allows flexibility in dosing intervals. There is less long term safety data on alternative opioids.

Evidence levels III and IV

B **Morphine or diamorphine should be used to treat moderate to severe pain in patients with cancer.**

C **The oral route is the recommended route of administration and should be used where possible.**

B **A trial of alternative opioids should be considered for moderate to severe pain where dose titration is limited by side effects of morphine/diamorphine** *(see section 7.9)***.**

Additional opioids for moderate to severe pain are available other than those detailed. They have either a poorer side effect or pharmacokinetic profile or are not available in suitable pharmaceutical forms for treatment of pain in patients with cancer *(see Annex 8)*.

6.4 ACUTE ON CHRONIC PAIN

When acute on chronic pain occurs, urgent analgesia may be required, remembering that the normal breakthrough dose of analgesia for the individual is likely to be inadequate. In the acute pain situation retitration of opioid analgesia is usually necessary. This is achieved by substituting a normal release opioid for any slow release preparation. If nausea and vomiting accompanies the acute pain use the parenteral route.

☑ In acute on chronic pain any slow release preparation should be replaced by a normal release morphine substitute.

7 Use of opioids in treatment of moderate to severe cancer pain

Opioids should be used for control of pain in patients with cancer as indicated in the WHO analgesic ladder *(see section 5)*. This section considers dosage, formulations, side effects, and methods of administration of opioids.

7.1 OPIOID DOSE

The opioid dose required to control an individual's pain will depend on many factors and is not related to any one parameter.[129] Patients require a wide range of opioid doses.[130] For these reasons, it is necessary to titrate the dose of opioid against each patient's pain. Opioid side effects can be predicted and failure to minimise side effects, particularly sedation, will limit titration and therefore the level of analgesia which can be achieved *(see section 7.4)*.

Evidence level III

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

7.2 ORAL MORPHINE FORMULATIONS

The time to onset of effect of the different morphine formulations varies, as does the time to peak drug levels.[89]

Evidence level Ia

7.2.1 NORMAL RELEASE PREPARATIONS

Normal release morphine preparations have an onset of action of about 20 minutes and reach peak drug levels on average at 60 minutes. The rapid onset of analgesia makes these preparations more suitable for use in initiating therapy for severe pain and for treating breakthrough pain *(see section 7.3.1)*. Normal release preparations must be given every four hours to maintain constant analgesic levels. When given every four hours these preparations will reach a steady plasma concentration and hence full effect within 12-15 hours. Thus the full effect of any dose change can be assessed at this time. In practice, during titration, dose adjustments are usually made every 24 hours unless the pain is more severe when adjustments may be made sooner.[131]

Evidence level IV

7.2.2 CONTROLLED RELEASE PREPARATIONS

Controlled release morphine preparations have a slower onset and later peak effect. Many of the twice daily preparations have an onset of action of 1-2 hours and reach peak drug levels at four hours. The once daily preparations have a slower onset and reach peak drug levels at 8.5 hours.[89] Controlled release preparations generally do not allow rapid titration for patients in severe pain, due to slow onset and the long dosing intervals.

Evidence level Ia

C **Where possible, titration should be carried out with a normal release morphine preparation.**

C **Normal release morphine preparations must be given every four hours to maintain constant analgesic levels.**

7.3 INITIATING AND TITRATING ORAL MORPHINE

Pain severity, age, and previous use of opioids for moderate pain will be considered when choosing the initial dose of opioid for moderate to severe pain. Extra care should be taken in patients with renal impairment.

The active metabolites of morphine are cleared through the renal system. Therefore in patients with renal impairment, morphine metabolites may accumulate and lead to toxicity. In patients with renal dysfunction, smaller doses of morphine and longer dosing intervals are required. It is good clinical practice to avoid controlled release morphine preparations in patients with renal dysfunction. Normal release morphine preparations are safer *(see section 7.2)* in the presence of renal impairment.

☑ Normal release opioid preparations should be used in patients with renal impairment.

When moving up from step 2 of the analgesic ladder, start the patient on normal release formulation of morphine sulphate 5-10 mg orally, every four hours.[128] A double dose may be given at bed-time and the overnight dose is then unlikely to be required.[132]

Evidence level IV

C **When initiating normal release morphine, start with 5-10 mg orally at four hourly intervals, unless there are contraindications.**

7.3.1 BREAKTHROUGH ANALGESIA

It is established practice when using morphine for cancer pain to prescribe one sixth of the total daily morphine dose to be taken at any time for breakthrough pain.[128] Breakthrough pain is defined as an unexpected increase in pain to greater than moderate intensity, occurring on a baseline pain of moderate intensity or less.[60]

Evidence level IV

C **Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of a normal release morphine.**

C **Breakthrough analgesia should be one sixth of the total regular daily dose of oral morphine.**

C **Breakthrough analgesia should be administered at any time outwith regular analgesia if the patient is in pain.***

☑ *Following the delivery of oral breakthrough analgesia wait 30 minutes to assess the response. If pain persists, repeat analgesia and reassess in a further 30 minutes. If pain still persists, full reassessment of the patient is required.

☑ Careful explanation of the correct use of breakthrough analgesia to carers and patients is necessary.

☑ Normal release morphine can be used for predictable movement-related pain. Where possible it should be used 30 minutes before movement.

7.3.2 DOSE TITRATION

Each day assess the pain control, degree of side effects and total amount of morphine required, including breakthrough doses, in the previous 24 hours. Divide the total amount required in the previous 24 hours by six. Prescribe this dose every four hours and alter the breakthrough analgesia dose accordingly (this is the same as the four hourly dose) i.e. one sixth of the total daily regular morphine dose.

If a patient is unable or unwilling to use breakthrough doses but is still in pain the dose of normal release morphine prescribed four hourly should be increased. The increase depends on the individual but is usually in 30-50% increments.

The rate of titration of morphine may be limited by drowsiness and in some patients longer is required to become tolerant to this effect before escalation of dose can be continued. Opioid responsiveness is a continuum and while a trial of opioids is required in all cases of moderate to severe cancer pain, some pains (e.g. neuropathic) do predictably require larger doses of opioids. However, the side effect profile associated with larger doses can restrict dose titration and hence limit analgesia. Careful titration with opioids is necessary and in such situations allow time for tolerance to develop to side effects, prior to increasing the dose.

Care should be taken when calculating a new regular dose for patients who are pain free at rest but have pain on movement. If all the analgesia for this incident pain is incorporated into the new regular morphine dose, such patients could be rendered opioid toxic. In particular, they will be rendered excessively sleepy at rest. This is because pain is a physiological antagonist to the sedative and respiratory depressant side effects of opioids. In such cases, optimum analgesia is achieved by maximising background analgesia, anticipatory analgesia for movement related pain, maximum use of non-opioid and adjuvant analgesics and consideration of other treatment modalities such as radiotherapy, anaesthetic nerve blocks, and stabilising surgery.[133]

7.3.3 CONVERTING TO CONTROLLED RELEASE PREPARATIONS

The same level of analgesia can be achieved by giving the total daily amount of normal release morphine as controlled release morphine.[134,135] When pain is controlled, add up the total daily dose of normal release morphine the patient is receiving and give this dose as a once daily controlled release preparation, or divide the total dose by two and give this dose as a twice daily controlled release preparation.

Evidence level Ib

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

☑ In addition to the controlled release morphine preparation continue to prescribe the appropriate dose of normal release morphine preparation as breakthrough analgesia.

When converting from normal release morphine to slow release preparations there is no need to administer a normal release formulation at the same time as the first slow release dose.[136]

Evidence level IIa

B **When transferring a patient from four hourly normal release morphine to a controlled release preparation start the controlled release preparation at the time the next normal release morphine formulation dose is due and discontinue the regular normal release morphine.**

7.4 PREDICTABLE SIDE EFFECTS OF MORPHINE AND OTHER STRONG OPIOID ANALGESICS

Opioids have predictable side effects. If these are not prevented or minimised, titration of analgesics will be limited. Sedation is the common limiting side effect to opioid analgesia and can cause a 'pseudo'-pharmacological ceiling dose. There may be some differences in side effect profiles between different opioids. The following are the most common side effects.

7.4.1 CONSTIPATION

The majority of patients taking opioids for either mild or moderate to severe pain will develop constipation. Little or no tolerance develops. The best prophylactic treatment for preventing opioid induced constipation is a combination of stimulant and softening laxatives.[137, 138]

Evidence level III

B **Patients receiving an opioid must have access to regular prophylactic laxatives. A combination of stimulant and softening laxative will be required.**

7.4.2 NAUSEA AND VOMITING

In clinical practice it appears that in opioid naïve patients, 30-60% will develop nausea and/or vomiting. Tolerance in the majority of patients usually occurs within 5-10 days. Patients commencing opioids should have access to antiemetics. A dopamine antagonist such as metoclopramide 10 mg tds (which is also prokinetic) or low dose haloperidol 1.5 mg nocte will be effective.

☑ Patients commencing an opioid for moderate to severe pain should have access to a prophylactic antiemetic to be taken if required.

☑ If a patient remains nauseated and/or continues to vomit, and if gastroparesis is excluded, the parenteral (most commonly subcutaneous or rarely intravenous) or transdermal route should be used for drug delivery until the patient stabilises *(see sections 7.8 and 7.9.1)*.

7.4.3 SEDATION

This can occur in the first few days of regular opioids for moderate to severe pain and subsequently if the dose is increased. This effect is augmented by concomitant use of other medication with central nervous system depressant effects.

☑ Patients receiving opioids for moderate to severe pain for the first time should be warned that sedation may occur and be advised of the risks of driving or using machinery.

☑ The use of other sedative drugs or drugs with sedative side effects should be rationalised.

7.4.4 DRY MOUTH

This usually occurs and the effect is augmented by concurrent medication with a similar side effect. Patients should be encouraged to take regular sips of cool water.

☑ All patients should be educated on the need for, and methods to achieve, good oral hygiene.

☑ The use of other drugs which can cause dry mouth, especially those with anti-cholinergic side effects, should be rationalised.

7.4.5 LESS COMMON SIDE EFFECTS OF OPIOIDS

Health professionals should be alert to the possibility of less common side effects developing, such as hypotension, respiratory depression, confusion, poor concentration, gastroparesis, urinary hesitancy or retention and itch.

7.5 OPIOID TOXICITY

There is wide individual variation in the dose of opioid that causes toxicity. The ability to tolerate a particular dose depends on the degree of opioid responsiveness of the pain, prior exposure to opioids, rate of titration of the dose, concomitant medication and renal and hepatic function.

Opioid toxicity can present as subtle agitation, seeing shadows at the periphery of the visual field, vivid dreams, nightmares, visual and auditory hallucinations, confusion and myoclonic jerks. Agitated confusion may be misinterpreted as uncontrolled pain and further opioids given. The sedated patient may then become dehydrated with resultant renal impairment. For opioids with significant active metabolites which are excreted via the kidney, metabolites will accumulate and may cause further toxicity in patients with renal impairment. The presence of opioid toxicity is an indication that the opioid dose is too high for the patient at this particular time, and it may warn of developing renal dysfunction.[139]

Evidence level IV

☑ Patients on opioids for moderate to severe pain should be monitored closely for signs of opioid toxicity. If this is present, advice from a palliative medicine specialist is advised.

C **Opioid toxicity should be managed by reducing the dose of opioid,* ensuring adequate hydration and treating the agitation/confusion with haloperidol 1·5-3 mg orally or subcutaneously. This dose can be repeated hourly in the acute situation.**

* *The degree of dose reduction depends on the clinical strategy, renal function, and responsiveness of the patient to opioids.*

7.6 PHARMACOLOGICAL TOLERANCE

Clinically relevant pharmacological tolerance to opioid analgesia does not occur in chronic cancer pain management. Increases in analgesia usually coincide with disease progression.[140]

Evidence level III

B **Initiation of opioid analgesia should not be delayed by anxiety over pharmacological tolerance as in clinical practice this does not occur.**

7.7 PHYSICAL AND PSYCHOLOGICAL DEPENDENCE

Psychological dependence on opioids (addiction) generally does not occur in cancer patients experiencing pain.[141]

Evidence level III

C **Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence.**

B **Patients should be reassured that they will not become psychologically dependent on their opioid analgesia.**

Physical dependence on chronically administered opioids may occur in cancer pain patients. Sudden discontinuation of opioid therapy may lead to a physical withdrawal syndrome,[142] which can be treated by administering a small dose of the opioid in question. However, abrupt discontinuation of opioids does not always produce this syndrome.[143]

Evidence levels III and IV

7.7.1 OPIOIDS AND DRUG ABUSERS

Some drug abusers will develop malignancies. The prescription of analgesia in such cases nearly always results in anxiety and tension on all sides. Inadequate prescription of opioids in such cases will result in drug-seeking behaviour for pain relief, commonly referred to as pseudoaddiction. A common sense approach is to accept background drug maintenance therapy, e.g. a methadone maintenance programme, and to titrate the most appropriate opioid analgesic along with NSAIDs and adjuvant analgesics as appropriate.

Knowledge of the pharmacokinetic/pharmacodynamic effects of the therapeutic opioid used (most commonly morphine) will usually guide the prescriber on the question of opioid titration. If the pain is opioid responsive, prescription of opioid should lead to improved function and less pseudoaddiction. Less opioid-responsive pains should be dealt with in the same way as in the non-drug abuser.

☑ Opioid drug abusers who develop pain from their cancer should receive adequate doses of opioid analgesic.

7.8 PARENTERAL ADMINISTRATION

When patients with moderate to severe pain are unable to take opioids by mouth, delivery by subcutaneous continuous infusion is effective.[144, 145] This avoids the need for repeated injections which may be painful. In addition the subcutaneous route can be used for prolonged periods of time.[146] Indications for using the parenteral route are inability to swallow nausea and/or vomiting, gastrointestinal obstruction and any pathology limiting gastrointestinal absorption. In situations where pain control has been stable, fentanyl may be administered transdermally *(see section 7.9.1)*. Uncontrolled pain is not an indication for using the parenteral route if further titration by the oral route is possible. If a breakthrough injection is needed, the subcutaneous route is less painful than the intramuscular route.

Evidence level III

The infusion devices most often used to deliver subcutaneous infusions are portable syringe drivers *(see section 7.8.4 for risks associated with use of a syringe driver)*. While the design of the most commonly used devices, the Graseby MS16A and MS26 confer many advantages, they only deliver a maximum volume of 30 ml per infusion. This volume restriction limits the amount of morphine sulphate that can be delivered to a patient *(see Annex 9)*, as one gram of morphine sulphate requires 16 ml of water for injection to dissolve.[147] One gram of diamorphine hydrochloride dissolves in 1.6 ml water for injection[148] and therefore almost any dose of diamorphine required can be incorporated into the volume available.

Evidence level IV

B **Patients requiring parenteral opioids should receive the appropriate dose of diamorphine via the subcutaneous route.**

☑ Transdermal fentanyl is an effective analgesic for severe pain and can be used in patients with stable pain who are unable to take oral medication *(see section 7.9.1)*.

7.8.1 CONVERTING FROM ORAL MORPHINE TO SUBCUTANEOUS DIAMORPHINE

From clinical practice, subcutaneous diamorphine is approximately three times as potent as oral morphine. To convert from the oral to the subcutaneous route, add up the oral morphine requirements, both regular and amount of breakthrough used in the previous 24 hours. Divide this dose by three. This dose may need to be adjusted prior to administration according to the clinical situation. Prescribe the calculated amount of diamorphine over 24 hours as a continuous subcutaneous infusion.[128]

Evidence level IV

C **To calculate the 24 hour dose of subcutaneous diamorphine divide the total 24 hour oral dose of morphine by three. Administer this dose of diamorphine subcutaneously over 24 hours.**

C **When converting from oral to subcutaneous diamorphine remember to prescribe a subcutaneous breakthrough dose which should be one sixth of the total daily dose of regular subcutaneous diamorphine.**

☑ If the patient's pain is controlled, start the continuous infusion when the next dose of oral morphine is due.

☑ If pain is uncontrolled, start the infusion as soon as possible and give a breakthrough dose of diamorphine immediately.

☑ Prescribe breakthrough analgesia (to be given at anytime by subcutaneous bolus injection) at a dose of one sixth of the total daily dose of subcutaneous diamorphine. Alternatively, patients able to continue taking small amounts orally can continue to take their oral equivalent morphine breakthrough dose.

To adjust the dose of diamorphine required, assess the pain control, prevalence of side effects and total amount of diamorphine required in the previous 24 hours (continuous infusion and breakthrough doses). This is the new dose of diamorphine required over 24 hours. Remember to adjust the dose of breakthrough diamorphine to one sixth of the new total daily dose of diamorphine.

Care should be taken when calculating a new regular dose for patients who are pain-free at rest but have pain on movement. If all the 'breakthrough' analgesia is incorporated into the new 24-hour diamorphine dose, such patients could be rendered opioid-toxic *(see section 7.3.2)*. Maximise background analgesia, anticipatory analgesia for movement related pain, use of non-opioid and adjuvant analgesics, and consider other treatment modalities such as radiotherapy, anaesthetic nerve blocks, and stabilising surgery.[133]

Evidence level IV

7.8.2 CONVERTING FROM A CONTINUOUS SUBCUTANEOUS DIAMORPHINE INFUSION TO ORAL MORPHINE

In situations where a patient regains the ability to take medication orally conversion from subcutaneous delivery to the oral route is usually appropriate. The dose of oral morphine is two (if pain is stable) or three (if pain control is not satisfactory) times that of the 24-hour dose of subcutaneous diamorpine. A controlled released preparation should be used if the pain is stable.[128]

Evidence level IV

C **To calculate the 24 hour dose of oral morphine required, multiply the total daily dose of subcutaneous diamorphine being administered by two (if pain is stable) or three (if pain control is not satisfactory). If pain is stable, administer this as a controlled release preparation.**

C **Analgesia for breakthrough pain should be prescribed as a normal release oral morphine preparation at one sixth of the total daily dose of oral morphine.**

☑ Stop the infusion as the first dose of modified release preparation is given.

☑ Adjust the dose depending on the clinical response.

7.8.3 DRUG STABILITY AND COMPATIBILITY

The small volume of infusate used in syringe drivers means that the drugs delivered may be very concentrated. Often the patients require other drugs to be administered concomitantly via the subcutaneous route, with the potential for drug incompatibilities.[149] Avoid administering irritant drugs subcutaneously, e.g. diazepam, chlorpromazine, prochlorperazine. A list of published or peer reviewed stability studies is provided at Annex 9.

Evidence level IV

C **Advice on stability of commonly used drug combinations for continuous subcutaneous infusion should be available to staff who prepare these infusions.**

C **Advice on the use of other combinations should be taken from palliative care specialists.**

7.8.4 RISKS INVOLVED IN USING PORTABLE SYRINGE DRIVERS

Although portable syringe drivers have unique advantages over other infusion devices available at present, their use is not free from risk. Incorrect use of Graseby MS16A and Graseby MS26 syringe drivers have been associated with patient deaths.[150, 151]

Evidence level III

Many of the errors have occurred due to similarities between the two models. Ignorance concerning other aspects of using such devices also exists. For example, one press of the boost button on the Graseby MS26 syringe driver delivers only about 1/200th of the total daily dose: far short of the one sixth required to treat breakthrough pain. There is also no lock-out on the boost button, allowing the contents of the syringe to be delivered in a very short period of time.

Guidelines for safe systems of infusion device management and use were issued by the Scottish Executive Department of Health in 1995. These outlined the need to have clearly defined management structure which encompasses: device registers, staff training, prescribing and administration guidelines, documentation, maintenance, procurement.

Evidence level IV

C **All staff using syringe drivers, including community-based health care professionals, must be fully trained in their correct use.**

C **At the point of use, staff should have access to manufacturer's instructions for any infusion device used to deliver continuous subcutaneous infusions of opioids for moderate to severe pain.**

C **Safe systems for use and management of syringe drivers must be in place as detailed in guidance issued by the Scottish Executive Department of Health.**

7.9 ALTERNATIVE OPIOIDS SUITABLE FOR THE TREATMENT OF MODERATE TO SEVERE CHRONIC PAIN

Changing opioids is rarely a solution to poorly controlled pain except where high doses are necessary and the first opioid is causing unacceptable side effects. Some evidence exists to suggest variation in the intensity of side effects of different opioids. The rationale for the use of these opioids is that for an individual patient these drugs may have a better therapeutic index than morphine.[153, 154]

Evidence levels Ib and III

The alternative opioids for moderate to severe pain in patients with cancer have all been shown to be effective analgesics. However there is no evidence at present of any superior clinical analgesic effect for these agents over morphine. These alternative opioids can be tried in patients with opioid sensitive pain who are unable to tolerate morphine side effects.[155]

Evidence level III

B **Alternative opioids can be tried in patients with opioid sensitive pain who are unable to tolerate morphine side effects.**

Equi-analgesic doses of alternative opioids can vary between individuals and within individuals over time. This is because the potency of an opioid in an individual will vary with a number of factors e.g. the type of pain, renal function, and previous opioid exposure. Therefore theoretical equianalgesic doses can only be taken as an approximate guide when transferring patients from one opioid to another. Careful clinical observation is required during such transfers.

7.9.1 TRANSDERMAL FENTANYL

Fentanyl is a powerful μ-receptor agonist. It is indicated in patients with stable pain who have difficulty or pain when swallowing, in patients who have unacceptable toxicity from morphine, in patients with persistent nausea or vomiting, and in gastrointestinal obstruction.

Transdermal fentanyl has been shown to have similar clinical efficacy in pain relief as morphine.[153, 154] It is formulated in a patch delivery system. The patch is generally replaced every 72 hours.[156] It has a lag time of 6-12 hours to onset of action[156] and after initiation of patch usage, any subsequent increase in dose takes 36-48 hours before steady state drug levels are achieved.[157] Drug plasma levels show little fluctuation at a regular dose. Patch size should not be increased for at least 48 hours until peak blood levels are reached. Therefore titration is slow and for unstable pain states the patch will not be appropriate. It is suitable for the control of stable pain.[156]

Evidence levels Ib and III

There is growing evidence that in some patients, fentanyl causes less constipation than morphine.[153, 158]

Evidence levels Ib and IV

B **Transdermal fentanyl is an effective analgesic for severe pain and can be used in patients with stable pain states as an alternative to morphine.**

When the transdermal fentanyl patch is removed, a subcutaneous depot remains. Serum fentanyl concentrations decline gradually, falling by 50% in 16 hours (range 13-22 hours).[159] This means extra care must be taken if transferring to other opioids. Particular care should be taken when patients already on transdermal fentanyl are commenced on a subcutaneous diamorphine infusion. This may be required when the pain state becomes unstable. Small amounts of subcutaneous diamorphine will be required until the fentanyl clears from the system and this can take up to 24 hours. In patients close to death, the patch should be left *in situ* and additional analgesia given by normal release oral morphine or intermittent or continuous subcutaneous diamorphine as dictated by the clinical situation.

Evidence level IV

As with all opioids, knowledge of the pharmacological profile of transdermal fentanyl is essential to ensure appropriate selection of patients and safe use.

☑ Prior to prescribing or transferring from transdermal fentanyl, full reference should be made to the manufacturer's literature or advice sought from a pain relief specialist.

7.9.2 HYDROMORPHONE

Hydromorphone is a powerful μ-receptor-agonist and is effective in achieving pain control in patients with cancer.[160] It may be useful where patients have persistent drowsiness and cognitive impairment despite careful titration with morphine.[155] Hydromorphone is available as both normal release and controlled release capsules, allowing titration as described for oral morphine. Hydromorphone is approximately 7.5 times as potent as morphine[160] and has similar pharmacokinetic properties.

Evidence levels Ib and III

B **Hydromorphone should be considered as a useful alternative in patients if morphine is causing cognitive impairment or where morphine is poorly tolerated.**

7.9.3 METHADONE AND PHENAZOCINE

Methadone is an effective analgesic.[161] Variation in half life between patients and also for each patient with time makes titration difficult.[162] Advice from specialists in palliative care should be sought concerning dose conversion and titration.

Evidence levels III and IV

Phenazocine has only one formulation and strength which makes titration difficult but it may be of use if patients suffer persistent confusion with morphine.[163]

Evidence level IV

☑ If methadone is prescribed, specialist advice should be sought concerning dose and strategy for titration.

7.9.4 OXYCODONE

Oxycodone is a powerful μ-receptor agonist and in equivalent doses is as effective as morphine in achieving pain control in patients with cancer.[164, 165, 166] Oxycodone is available in both normal release and controlled release formulations. The oxycodone:morphine ratio is 1:2.[167] Oxycodone has a more predictable bioavailability than morphine (15-65% for morphine vs. 60-87% for oxycodone). Controlled release oxycodone has a biphasic pharmacokinetic release profile showing two peaks after oral administration. This allows onset of analgesia within an hour of oral ingestion and an analgesic duration of 12 hours. This release pattern may be clinically useful.

Evidence levels Ib and IIb

B **Oxycodone should be considered as an alternative in patients unable to tolerate morphine.**

7.10 MANAGEMENT OF POSTOPERATIVE PAIN IN PATIENTS ALREADY ON OPIOIDS

The team looking after the patient postoperatively must be aware whether the patient was taking opioids preoperatively. Patients taking opioids preoperatively need a larger than normal dose of opioids postoperatively. Patients are commonly given the standard postoperative analgesia and suffer pain as a result. If possible a pain specialist should be consulted. A patient-controlled analgesia (PCA) system should be used, set with a larger background and bolus dose than usual based upon the preoperative opioid dosage and a short lockout time. The use of NSAIDs in conjunction with opioids should be considered, as long as there are no contraindications.

☑ Patients taking opioids preoperatively should be managed in a high dependency unit postoperatively.

8 Adjuvant analgesics

These drugs are used in combination with opioids and may result in synergistic effects producing better pain relief at lower dose of opioids, hence the patient may experience fewer opioid side effects.

8.1 TRICYCLIC ANTIDEPRESSANTS AND ANTICONVULSANTS

Tricyclic antidepressants are effective in relieving neuropathic pain.[89] Despite the possible differences in underlying pain causation, different tricyclic antidepressants are similarly effective in the different pain syndromes. There are no significant differences in efficacy between the different tricyclic antidepressants.

The anticonvulsants carbamazepine, phenytoin, sodium valproate, clonazepam, and gabapentin are effective in treating neuropathic pain of non-malignant aetiology. Benefit was independent of pain characteristics.[89] Gabapentin is licensed for the treatment of neuropathic pain and recent RCTs have demonstrated its efficacy.[168, 169, 170]

Evidence levels Ib and Ib

There is no measurable difference in the analgesic benefit of the two drug classes (tricyclic antidepressants or anticonvulsants) in neuropathic pain or in the number of patients needed to treat before a minor or major adverse effect occurs.[89]

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

In clinical practice, tricyclic antidepressants appear better tolerated than anticonvulsants. The choice of antidepressant should be based on relative contraindications, possible drug interactions and risk of side effects for each patient. Tricyclics and anticonvulsants may be prescribed simultaneously. It is good clinical practice to introduce only one drug at a time.

There is a lack of evidence for efficacy of Selective Serotonin Reuptake Inhibitors (SSRI) antidepressants for treating neuropathic pain.

8.2 STEROIDS

There is some evidence for the use of steroids as analgesics in patients with cancer pain. Clinical experience shows steroids to be useful adjuvant analgesics for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, spinal cord compression and hepatic capsular pain. High dose dexamethasone up to 16 mg/24 hours may be required. The dose and duration depends on the clinical response to treatment. The last dose should be given at 6 pm as insomnia may be a problem if given later.[171]

Evidence level IV

C **A therapeutic trial of oral high dose dexmethasone should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, spinal cord compression, or hepatic capsular pain (unless there are contraindications). In some clinical situations (e.g. if the patient is vomiting) it may be necessary to use the intravenous route.**

8.3 MEXILETINE

Mexilitene does appear to be effective in reducing pain associated with nerve damage but it carries a high risk of serious side effects.[89]

Evidence level Ia

A **Mexiletine should not be used routinely as an adjuvant analgesic.**

8.4 KETAMINE

Ketamine has been used as an anaesthetic for 40 years. However at sub-anaesthetic doses it acts as an analgesic. This effect is chiefly mediated by blocking the N-methyl-d-aspartate (NMDA) receptors in the dorsal horn.[172] The NMDA receptor is thought to be activated in clinical states where allodynia, hyperalgesia and hyperpathia are present.[173]

Evidence level IV

The use of ketamine as an analgesic is increasing in pain clinics and specialist palliative care units. It is generally administered intravenously or subcutaneously. Ketamine may be indicated in neuropathic pain states, ischaemic pain, in acute inflammatory disorders and phantom limb pain.[174] If successful ketamine will restore the patient's morphine sensitivity and opioid toxicity may occur.

Ketamine may cause transient hypertension and so caution is required if there is a history of hypertension, cardiac failure or cerebrovascular accident. Hallucinations, dysphoria and vivid dreams may occur when using ketamine.

☑ The use of ketamine as an analgesic should be supervised by a specialist in pain relief or a palliative medicine specialist.

9 Systemic anti-cancer therapy

Response to systemic therapy used for pain control is likely to be delayed. Patients should also receive appropriate analgesics according to the principles outlined in section 5.

9.1 CHEMOTHERAPY

Palliative chemotherapy has been documented as being effective in the management of patients with pain from metastatic disease.[175] Selection of appropriate chemotherapy should be made by an oncologist and its effect reviewed regularly by an oncologist. Where it is being used primarily for pain relief it is generally less appropriate than radiotherapy or endocrine therapy. The reasons are:

Evidence level IV

- Chemotherapy may already have been used earlier in the course of the disease.
- The response rates to chemotherapy for the common cancers with metastatic or locally advanced disease are relatively poor.
- Patients will have poorer performance status and as a consequence drug toxicity may be enhanced.

9.1.1 BREAST CANCER

Patients presenting with locally advanced or inflammatory breast cancer or patients with metastatic disease may experience pain. In patients with symptoms mainly from widespread bone metastases and a reasonable performance status chemotherapy may achieve excellent palliation[175] This area is discussed in the SIGN/SCTN guideline on breast cancer[176] *(see also section 9.2.1 below)*.

☑ Patients with locally advanced or inflammatory breast cancer should be treated with systemic treatment as part of multimodality therapy.

☑ Chemotherapy should be considered in patients with breast carcinoma with widespread painful bone metastases and a reasonable performance status.

9.1.2 LUNG CANCER

Chemotherapy can be effective and provide palliation for symptomatic extensive disease from small cell lung cancer (SCLC) causing pain, including cerebral metastases. This area is covered in the SIGN/SCTN guideline on lung cancer.[177]

9.2 ENDOCRINE THERAPY

Endocrine treatment is used frequently in two tumour sites: breast and prostate cancer. Endocrine therapy has the advantage of being much less toxic than chemotherapy but the response rates for palliation in breast cancer are usually lower and time to response is slower. This is due to patients having had previous treatment or who have endocrine non-responsive disease. This relatively poor and slow response rate may be unacceptable when the aim is palliation of pain.

9.2.1 BREAST CANCER

Tamoxifen is recognised as first line endocrine therapy for breast cancer[178] *(see the SIGN/SCTN guideline on breast cancer[176])*. Most patients already will have received this treatment.

The new aromatase inhibitors (e.g. anastrozole, letrozole) are replacing standard second line therapy (after tamoxifen), due to longer duration of response, survival advantages and less side effects.[179-182]

Evidence level Ib

A **In patients with metastatic breast cancer who have progressive disease despite prior tamoxifen, the use of specific aromatase inhibitors such as anastrazole and letrazole should be considered.**

9.2.2 PROSTATE CANCER

Hormonal therapy is recommended for newly diagnosed patients with metastatic prostatic cancer. Medical castration using luteinising hormone-releasing hormone (LHRH) analogues is gradually replacing surgical castration because of patient preference and improved quality of life.[183]

Evidence level III

Many studies have examined maximum androgen blockade. A meta-analysis of this using nonsteroidal antiandrogens with LHRH or orchidectomy has produced inconsistent results when the end point has been survival benefit.[184] Similarly, when the steroid anti-androgen cyproterone acetate was combined with LHRH analogue, there was no advantage in terms of time to progression compared with monotherapy although side effects caused by LHRH analogue treatment alone were reduced.[185]

Evidence levels Ia and Ib

C **Primary endocrine therapy should be considered for all patients presenting with prostatic carcinoma and painful bone metastases.**

C **Maximum androgen blockade should be considered for management of patients with prostate cancer with worsening bone pain or progression on current single agent endocrine therapy.**

10 Radiotherapy

10.1 GENERAL

Radiotherapy is usually considered the most effective oncological treatment modality in relieving pain. It is especially effective in relieving pain due to bone metastases and when used for this indication produces few side effects. A systematic review of the literature examined the evidence for using radiotherapy for painful bone metastases from all cancer sites and reported the difficulty in performing clinical trials in this patient group.[186] Guidelines for the management of metastatic bone disease in breast cancer have been published,[187] and the principles they convey can be extended to bone metastases occurring from other primary tumours.

Evidence level Ia

10.2 BONE METASTASES

A systematic review of the use of radiotherapy for bone pain showed complete pain relief at one month in 27% of patients, and at least 50% relief in an additional 42% of patients at any time in the duration of the trials included.[186] Another systematic review on this subject highlighted difficulties in conducting these studies due to different treatments administered, variable fields and wide variation in performance status of patients.[188] It listed studies giving complete pain relief in the range 21-88%. Radiotherapy using simple techniques and short fractionation should be employed.[187, 189] For wider fields, increased fractionation should be employed with anti-emetics. If the cause of the pain is mechanical instability, surgical stabilisation should be carried out if possible, and will generally provide pain relief. [133]

Evidence levels Ia, III and IV

C **Radiotherapy should be considered for painful bone metastases.**

C **The management of mechanical bone pain is more complex and if the patient is fit enough should involve consultation with an orthopaedic surgeon.**

10.2.1 PROSTATE CANCER

For prostate cancer, radioactive strontium is effective for pain control and may protect against the development of further painful bone metastases.[190] However, strontium may take up to twelve weeks to give symptomatic relief. Therefore local radiotherapy should be considered for the main site of pain at the same time as administration of strontium. Hemi-body irradiation can also reduce the number of sites of bone pain.[191]

Evidence levels Ib and IV

B **Radioactive strontium should be considered for the management of pain due to widespread bone metastases from prostatic carcinoma.**

10.3 OTHER SITES

10.3.1 BRAIN METASTASES

C **High dose steroids and radiotherapy should be considered for headache due to cerebral metastases.**

(See section 8.2)

10.3.2 SPINAL CORD COMPRESSION

This condition may be associated with pain and is considered an oncological emergency. The majority of patients who develop spinal cord compression suffer radicular pain for several weeks prior to overt expression of this condition.[192] Depending on clinical factors, the patient should be treated with high dose steroids, analgesics, surgery, radiotherapy or a combination of modalities. Spinal cord compression requires urgent investigation and intervention.

Evidence level IV

☑ Urgent treatment should be given for all patients with spinal cord compression.

10.3.3 PANCOAST TUMOUR

Management of patients with pancoast tumours is discussed in the SIGN/SCTN lung cancer guideline.[177]

11 Bisphosphonates

11.1 GENERAL

Radiotherapy remains the intervention of choice for localised bone pain but many patients have widespread poorly localised bone pain while others will experience recurrence of pain in previously irradiated skeletal sites. Bisphosphonates provide an alternative treatment approach to the management of these patients and are of proven value in multiple myeloma and bone metastases from breast cancer.

11.2 MULTIPLE MYELOMA

This is characterised by a marked increase in osteoclast activity and proliferation. Several placebo controlled randomised trials of bisphosphonate use have been published.[193, 194] These indicate that bisphosphonates are superior to placebo in patients with multiple myeloma and reduce bone events, pain and hypercalcaemic episodes.

Evidence level Ib

A **Bisphosphonate treatment should be considered for all patients with multiple myeloma.**

11.3 BREAST CANCER

There is evidence that intravenous bisphosphonates are of benefit in patients with severe bone pain which is unresponsive to strong analgesics and is too widespread for local radiotherapy.[195, 196] Repeated intravenous infusions of clodronate (two-weekly) or pamidronate (four-weekly) can be given, the length of treatment based on the duration of response. Further guidance is awaited from dose, schedule and duration studies. There are several placebo controlled randomised trials showing significant reduction in skeletal morbidity including bone pain.[197, 198] Again, clodronate and pamidronate were used. The duration of therapy is unclear.

Evidence level Ib

A **Bisphosphonates should be considered in the management of breast cancer patients who have pain due to metastatic bone disease.**

(See the SIGN/SCTN guideline on breast cancer.[176])

11.4 OTHER NEOPLASMS

Skeletal metastases from prostate cancer are osteoblastic. There are no large scale double blind trials to advise on the use of bisphosphonates in metastatic prostatic cancer. Phase III studies are underway. There is no data to support the use of bisphosphonates in patients with osteolytic bone metastases from other primaries.

☑ Bisphosphonates should not be used in the management of other bone metastases outwith the context of a clinical trial.

12 Interventional techniques for the treatment of pain from cancer

12.1 GENERAL

Interventional techniques can be used to provide long term pain relief for patients whose pain is not controlled by simpler methods, such as systemic drug therapy. They can also be used for short term analgesia for patients with severe incident pain, or in other situations where more definitive treatment is awaited.

In practice the doctor to whom the patient is referred is the one who will make the decision about whether a procedure is appropriate and which one to advise. As in many other areas of medicine, a multidisciplinary approach is helpful. GPs, hospital and hospice doctors should ideally have close links with local pain clinics and neurosurgery departments. It is not necessary for the referring clinician to know details about the procedure, but it is helpful if they know the possibilities, limitations and what the procedure involves for the patient.

The level of evidence for the effectiveness of some of these treatments appears low. This does not mean that they are not effective, but reflects the difficulties of undertaking randomised controlled trials in this area of medicine. Many of these treatments are used because all other simpler methods have failed to relieve the patient's pain.

Case series are often the best evidence that we have, and even these tend to be relatively small numbers, because no one centre accumulates a large series of these patients. In the case of intraspinal opioids the technique is still evolving and there is therefore no evidence on some of the combinations of equipment and drugs currently used by some centres.

☑ Interventional techniques to relieve pain in patients with cancer should only be considered in the following circumstances:

(1) Standard treatments, such as systemic drug therapy (oral, transdermal, subcutaneous etc.) have been tried and failed. Failure may be due to insufficient pain relief or unacceptable side effects.

(2) Personal, psychological and social circumstances should have been evaluated.

(3) Other causes for incomplete analgesia should have been excluded.

(4) The patient should be fit enough for the procedure.

(5) The patient must be able to give informed consent.

(6) The patient's pain must be likely to respond to the procedure.

12.2 EPIDURAL AND INTRATHECAL DRUG DELIVERY SYSTEMS

By introducing opioids and/or local anaesthetic drugs into the epidural space or the cerebrospinal fluid it is possible to achieve profound analgesia with small doses and few side effects.[199, 200] This is because one of the main sites of action of opioids is in the spinal cord and small amounts of the drug delivered there will have a powerful effect. Local anaesthetics have an analgesic action in the spinal cord and potentiate the effect of the opioids there.

Evidence level III

Epidural and intrathecal opioid/local anaesthetic infusions undoubtedly can provide effective analgesia, but require skilled personnel (usually a pain clinic anaesthetist) to put the systems in place and then a certain level of care afterwards to monitor them. Catheters can be placed at any level of the spinal cord, although most commonly these techniques are used for pain in the lower part of the body. They are ideal for difficult abdominal or pelvic pain.

For short term use, epidural catheters can be placed percutaneously, and fixed either by secure taping or subcutaneous tunnelling. The drugs can then be delivered through a small pump, or a syringe driver. Patients can be ambulant and managed at home with these systems. However the primary care team must have the necessary training, knowledge and support.

In patients with a longer prognosis, but who have a continuing source of pain, intrathecal systems, which are fully implantable, have many advantages. These offer great freedom to the patient, as there is no external equipment and the pump only needs to be refilled every few weeks. Some of the pumps are programmable and offer great flexibility. They use a radiotelimetry system similar to cardiac pacemakers.

12.3 COELIAC PLEXUS BLOCK

In patients with upper abdominal pain coeliac plexus block provides analgesia for patients with pancreatic cancer or other upper abdominal malignancies. Thoracoscopic splanchnicectomy has been suggested as an alternative, but experience is still limited with this procedure.

A recent meta analysis confirms the efficacy of the technique,[201] although only two RCTs were found: a study of 20 patients which suggested that coeliac plexus block can provide analgesia equal to drug therapy with opioids and NSAIDs but with fewer side effects;[202] and a comparison of three different techniques of coeliac plexus block which showed that the techniques were successful in abolishing the pain of pancreatic cancer until death in 60-75% of patients.[203] Since this meta analysis, one further RCT has been published, which reached the same conclusions.[204]

Evidence levels Ia and Ib

A **In patients with upper abdominal pain, especially secondary to pancreatic cancer, coeliac plexus block should be considered.**

12.4 CORDOTOMY

This technique only treats pain on one side of the body. Bilateral cordotomy can be performed, but although this will stop pain on both sides of the body it does not affect midline pain and is generally associated with a higher incidence of side effects.[205]

Evidence level IV

Cordotomy may be performed as an open operation, or as a percutaneous procedure. The percutaneous procedure is more commonly used nowadays, and is performed in the cervical region at C1-2. The highest level of analgesia obtainable is about C4 which corresponds to the shoulder. Neck pain does not normally respond. Special care is needed in patients with impaired lung function, as percutaneous cervical cordotomy may cause some reduction in the expansion of the lung on the side of the procedure. This is obviously important in patients with lung tumours, who will commonly have pain and reduced lung function on the side of the tumour.

Cordotomy can provide complete analgesia in about 2/3 of patients.[206] If a patient has widespread pain, but one location where it is not controlled by simple measures, then cordotomy may be useful in controlling that pain. Other methods, such as drug therapy, will be needed after the cordotomy for the pains which lie outside the area covered by the cordotomy. The pain relief is not permanent, and the duration is variable. Pain relief will seldom last longer than one year in most patients. *Evidence level IV*

12.5 LESS FREQUENTLY USED NEUROSURGICAL TECHNIQUES

12.5.1 INTRA-VENTRICULAR DRUG DELIVERY SYSTEMS

In the same way that opioids can be delivered to the spinal cord, for facial and head pain a catheter can be inserted into the ventricles of the brain, and linked to a pump system.[207] *Evidence level IV*

12.5.2 REGIONAL ANAESTHETIC TECHNIQUES FOR SHORT TERM PAIN RELIEF

The use of these techniques in managing pain in patients with cancer is seldom reported in the literature and there are no reports involving more than a handful of patients and no adequate trials.

Regional anaesthetic techniques can be divided into central neural blocks (e.g. spinal or epidural anaesthesia), plexus blocks (e.g. brachial plexus block) or peripheral nerve blocks (e.g. femoral nerve block). These can be performed as single shot techniques, or a catheter can be inserted so that top ups can be given to allow prolonged use.

The help of a suitably skilled anaesthetist should be obtained.

12.5.3 CENTRAL NEURAL BLOCKS

Spinal and epidural anaesthesia can provide profound analgesia for problems such as pathological fractures or procedures such as painful dressing changes in the perineum or lower limbs, and manual disimpaction. If complete anaesthesia is required, then the attendance of fully trained staff with all the relevant monitoring and resuscitation equipment is mandatory. This restricts the use of these techniques in practice, as NHS Anaesthetic Departments do not have sufficient staff to allow the necessary flexibility.

12.5.4 PLEXUS BLOCKS

Brachial plexus block can be achieved by anaesthetising the nerves of the brachial plexus at the neck (interscalene approach), the shoulder (supraclavicular) or the armpit (axillary). This can provide anaesthesia of the upper limb and is routinely used for hand and arm surgery in many hospitals. It can be used for incident pain, such as painful dressings, or for longer term pain relief if a catheter is inserted into the sheath of the brachial plexus. The technique requires a relatively high degree of skill and has to be regularly practised to achieve consistently good results.

12.5.5 PERIPHERAL NERVE BLOCKS

Block of the femoral nerve can provide useful short term analgesia for femoral fractures. Although it appears an easy block, in practice it is difficult to achieve consistently good results.

Intercostal nerve block with local anaesthetic can provide good short term relief for pain from ribs or other chest wall problems. It appears easy, but the risk of pneumothorax is present, and more likely in unskilled hands. In the past doctors used phenol or alcohol to block intercostal and other peripheral nerves in the hope of achieving a long lasting block. This is no longer recommended because of the high incidence of neuralgia.

12.6 PROBLEMS AFTER INTERVENTIONAL TECHNIQUES

Patients taking large doses of opioids who have successful interventional treatments may encounter problems and will need careful supervision and monitoring.

If the opioids are continued at the same dose after a successful pain relieving procedure, side effects may occur. Pain seems to act as a 'physiological antagonist' to some opioid side effects, especially sedation and respiratory depression. If pain is controlled by interventional treatment respiratory depression can occur over a short timescale leading to respiratory arrest. To avoid this the dose of opioid should be reduced by approximately one third. The dose reduction depends on the level of pain relief and the amount of sedation or respiratory depression.

Physical withdrawal symptoms may occur if the opioids are stopped abruptly *(see section 7.7)*.

C **All professionals looking after patients with pain from cancer should be aware of the range of neurosurgical and anaesthetic techniques available for the relief of pain.**

C **All professionals looking after patients with pain from cancer should have access to a specialist pain relief service, able to offer the techniques described above.**

C **If a patient's pain is not controlled by other measures, then the advice of a specialist in pain relief should be sought, with a view to performing one of the above procedures.**

☑ After successful interventional procedures patients already on opioids should have the dose reduced by approximately one third.

☑ After interventional procedures patients on opioids should be carefully supervised for increased signs of opioid toxicity.

Annex 1

DETAILS OF LITERATURE SEARCH UNDERTAKEN FOR THE GUIDELINE

The evidence base for this guideline was synthesised in accordance with SIGN methodology.[208] A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group.

All searches covered systematic reviews, meta analyses, and randomised controlled trials. In areas where there is a paucity of sound randomised controlled trials, observational studies were also included. Initial searches covered the period from 1980 to 1997 and were updated during the course of the guideline development process to take into account newly published evidence.

Sections of this guideline related to drug therapies were based on a systematic review carried out for the NHS National Cancer Research and Development Programme[89] supplemented by searches conducted by development group members.

Searches on other issues were carried out on the Cochrane Library, Cancerlit, CINAHL, Embase, Healthstar, Medline, and Psychlit. Topics related to alternative therapies were additionally searched on the Allied & Alternative Medicine and Mantis databases. Psychosocial issues were also researched in the social science literature by a member of the guideline development group.

Annex 2

RECOMMENDATIONS FOR RESEARCH AND AUDIT

- Due to the ethical problems in conducting trials in patients with cancer pain, highlighted in the introduction to this guideline, research should be undertaken to establish appropriate methodologies for undertaking studies in this area.
- The incidence and types of cancer treatment related pain.
- Why is pain difficult to control in 20% of patients?
- The impact of changes in health care professionals' pre-registration training in principles of pain control should be assessed in terms of knowledge, attitudes, skills and patient outcomes.
- How the attitudes of health professionals, carers and patients affect the treatment options for pain control in cancer patients.
- Do cognitive pain management techniques have a role in the management of cancer pain?
- The role of psychological intervention in reducing anxiety and depression and the resultant effect on pain levels.
- The value of various psychological interventions in the management of pain in patients who are not significantly anxious and/or depressed.
- The benefits of including occupational therapists, physiotherapists and other professions allied to medicine in the multidisciplinary team managing pain control in cancer patients.
- The role of chaplains and other spiritual representatives in pain control.
- A comparison of antidepressants and anticonvulsants as adjuvant analgesics in controlling pain in cancer patients.
- The role of selective serotonin re-uptake inhibitors (SSRIs) in the control of neuropathic pain.
- The role of bisphosphonates in managing pain from bone metastases in cancer (other than breast cancer and multiple myeloma where the efficacy is already proven).
- The dose and duration of bishosphonate treatment in the management of pain from bone metastases.
- Stability data to support the admixing of drugs in small volume infusions.
- The effectiveness of locally applied opioids as analgesics for sites of local pain in inflamed tissues.
- Does combining NSAIDs and paracetamol produce synergistic analgesia compared to single agent prescribing?

Annex 3

MINIMUM CORE DATA SET

Data Item	Field Name	Coding Details
Patient Details		
Patient surname	PATSNAME	
Patient forename	PATSFNAM	
Date of birth	DOB	
Patient address	PATADD	
Patient postcode	PATPCODE	
Unit number (hospital patient identifier)	UNITNUM	
CHI number	CHINUM	
Named GP	GP	
GP practice code	GPPRACT	
Named consultant	CLINAM	Record GMC number
Hospital of consultant	HOSP	
Pain Assessment		
Assessment date	ASSDATE	
Pain level	PAIN	1 = None 2 = Mild 3 = Moderate 4 = Severe 5 = Patient not assessed
Assessment performed by	ASSESSMENT	1 = Patient 2 = Hospital doctor 3 = GP 4 = Nurse 5 = Carer
Prescription Details		
Date of prescription	DATEPRES	
Type of analgesic	ANALTYPE	1 = Opioid 2 = Non-opioid
Name (analgesic)	ANALNAME	
Dose (analgesic)	ANALDOSE	mg
Frequency (analgesic)	ANALFREQ	1 = < 4hrs 2 = Every 4 hrs 3 = Every 6hrs 4 = Every 12 hrs 5 = Every 24 hrs 6 = Every 72 hrs 7 = As needed
Route of delivery (analgesic)	ANALROUT	1 = Oral 2 = Subcutaneous injection 3 = Intravenous 4 = Syringe driver 5 = Transdermal 6 = Suppository
Breakthrough medication	BRKNAME	
Dose (breakthrough)	BRKDOSE	in mg
Number of breakthrough doses used in the past 24 hours	BRKFREQ	0 - 8
Route of delivery (breakthrough)	BRKROUT	1 = Oral 2 = Subcutaneous injection 3 = Intravenous 4 = Suppository 5 = Intramuscular
NSAID	NSAID	1 = Yes 2 = No 3 = Contraindicated
Laxative	LAXATIVE	1 = Yes 2 = No
Form completed by	FORM	1 = Hospital doctor 2 = GP 3 = Nurse 4 = Carer

Annex 4

SOURCES OF INFORMATION AND ADVICE FOR HEALTH PROFESSIONALS

Health professionals seeking information and advice about the control of cancer pain should contact their local specialist palliative care service or pain clinic.

For information on specialist palliative services in Scotland contact:

The Scottish Partnership Agency for Palliative and Cancer Care
1A Cambridge Street
Edinburgh
EH1 2DY

Tel: 0131 229 0538
Email: Office@spapcc.demon.co.uk
Website: http://www.spapcc.demon.co.uk

Publishes a quarterly update.

The Hospice Information Service at St Christophers
51-59 Lawrie Park Road
Sydenham
London
SE26 6DZ

Tel: 020 8778 9252
Email: his@stchris.ftech.co.uk
Website: http://www.kcl.ac.uk/kis/schools/kcsmd/palliative/his.htm

Publishes Hospital Information Services Directory (annual)

For information on pain clinics in Scotland contact:

The Pain Society
9 Bedford Square
London
WC1B 3RE

Tel: 020 7636 2750

Annex 5

PATIENT SUPPORT GROUPS AND INFORMATION

PHONE LINE INFORMATION SERVICES

Cancer BACUP (Scotland)	*Tel:*	0141 553 1553
	Freephone:	0808 800 1234
	Website:	http://www.cancerbacup.org.uk
Pain Association Scotland	*Tel:*	0131 312 7955
	Freephone:	0800 783 6059
Tak Tent Cancer Support Scotland	*Tel:*	0141 211 1930
Cancerlink	*Tel:*	0171 833 2818
	Freephone:	0800 132 905

READING MATERIALS

BACUP series:	**Feeling better: controlling pain and other symptoms of cancer**
Available from:	Cancer BACUP 3 Bath Place Rivington Street London EC2A 3JR
Cancerlink series:	**Living with cancer that cannot be cured** **The Directory of Cancer Self Help and Support (published annually)**
Available from:	Cancerlink 11-21 North Down Street London N1 9NB

Annex 6

KEY MESSAGES FOR PATIENTS

- Not all patients with cancer have pain.
- Patients with cancer who do experience pain should not accept uncontrolled pain as part of their condition.
- Most pain can be well controlled. In difficult cases the pain can at least be reduced in severity.
- A patient with cancer can experience pain due to non-cancer related illness.
- Increasing pain does not mean death is imminent.
- Patients and their carers should have a full explanation of how to take their medication including the indications for the drug, the name of the drug, how often to take it, how to deal with breakthrough and incident pain, and the possible side-effects of the drug.
- Patients with chronic pain should be prescribed regular analgesics with analgesic strength commensurate to the level of pain.
- Analgesics invariably produce constipation and prescribed laxatives should be taken as instructed.
- Patients should be informed of the availability of appropriate clinical trials. When this information is provided it should also be stated that there is no obligation for patients to participate in any trial.
- Barriers to the use of opioids for pain control are fear of tolerance or addiction. Starting morphine or another opioid early does not mean the dose will steadily increase to a very large dose and that if pain increases there will be no suitable analgesic available. Patients with cancer who have pain and are prescribed morphine-type analgesics do not develop psychological dependency. Being commenced on opioids does not mean death is imminent.
- A patient who is unhappy with their level of pain control has the right to ask to be referred to a palliative medicine physician or anaesthesist specialising in pain control. Requesting this will not affect how they are treated by their present physician.

Annex 7

SOME ADJUVANT ANALGESICS

Drug	Dosage	Indications	Main side effects
NSAIDS e.g. ibuprofen diclofenac	400-600 mg qid 50 mg po tds (sr 75 mg bd) 100 mg pr daily	Bone metastases Soft tissue infiltration Liver pain	Gastric irritation Gastric bleeding Fluid retention Headache Vertigo Renal impairment
Steroids e.g. dexamethasone	8-16 mg/day	Raised intracranial pressure Nerve compression Soft tissue infiltration Liver pain Bone pain	Gastric irritation if together with NSAID Fluid retention Confusion/agitation Cushingoid appearance Carbohydrate intolerance Oral candidiasis
Tricyclic Antidepressants e.g. Amitriptyline	25 mg nocte (starting dose) median effective dose: 75 mg nocte	Neuropathic pain	Sedation Dizziness Postural hypotension Dry mouth Constipation Urinary retention
Anticonvulsants e.g. Carbamazepine Gabapentin	200 mg nocte (starting dose) rising to 1600 mg (maximum dose) 300 mg/day rising to 1800 mg/day in three divided doses	Nerve pain Nerve pain	Vertigo Nausea Constipation Rash Drowsiness Dizziness Gastrointestinal upset

Annex 8

DRUGS AND PREPARATIONS THOUGHT NOT TO BE SUITABLE FOR THE TREATMENT OF MODERATE TO SEVERE CHRONIC PAIN IN PATIENTS WITH CANCER

Non-opioids	**Nefopam** - can cause troublesome sympathomimetic and anti-muscarinic side-effects.
Opioids for mild to moderate pain	**Compound preparations containing subtherapeutic codeine or dihydrocodeine doses per tablet** (i.e. less than 30 mg codeine or dihydrocodeine per tablet) e.g. Co-codamol, Co-dydramol, Co-codaprin - there is no evidence of their superiority over paracetamol alone
	Tramadol - *see section 6.2.*
Opioids for moderate to severe pain	**Buprenorphine** - is a partial agonist (mixed agonist/antagonist) and its ceiling effect prevents continuing titration if pain escalates.
	Dextromoramide - too short-acting for regular use. May be of some use in controlling incident pain. Is twice as potent as morphine and can be used sublingually.
	Dipipanone - only available in combination with cyclizine. Titration of analgesia would lead to cyclizine overdose.
	Meptazinol - 200 mg orally (4 times a day) is equivalent to 2 co-proxamol (4 times a day). Poor oral bioavailability means pain relief which can be achieved is limited. No reports of it being used subcutaneously.
	Nalbuphine and pentazocine - dose limiting psychomimetic effects. Mixed agonist/ antagonist which can precipitate withdrawal in patients physically dependent on morphine like drugs. Pentazocine is orally no more potent than paracetamol or aspirin.
	Papaveratum - effect depends largely on morphine content. No advantage over morphine. Aspav is a combination of aspirin 500 mg and papaveratum 10 mg.
	Pethidine - accumulation of metabolite norpethidine which is neurotoxic.

Annex 9

DRUG STABILITIES

NOTES ON USING TABLES OF DRUG MIXTURE STABILITIES

The following tables are separated into mixtures containing two or three drugs, ordered by diamorphine first, then the other drugs in alphabetical order.

The maximum dose for each drug in each syringe size is given. Provided the doses for every drug in the combination is less than or equal to these maximum values, then the mixture is stable for 24 hours. Above the maximum doses stated the solution is either unstable or has not been tested and it is not possible to say whether it is stable or not.

All drug mixtures should be protected from light where possible, as some of the drugs will degrade more rapidly in light.

Other drug combinations may be used at specialist palliative care centres. At present there is no stability data to support the use of these combinations. Where there is no alternative or the proposed combination provides a clear clinical advantage advice can be sought from these centres.

No information is given on the therapeutic uses for combinations given. For further clinical information, seek specialist advice.

The following combinations are not stable:

- Diamorphine, dexamethasone and methotrimeprazine
- Diamorphine, dexamethasone and midazolam
- Diamorphine, cyclizine and metoclopramide
- Octreotide and methotrimeprazine
- Octreotide and cyclizine
- Octreotide and dexamethasone
- Diamorphine, metoclopramide and ondansetron.

TWO DRUG COMBINATIONS FOR SUBCUTANEOUS INFUSION WHICH ARE STABLE FOR 24 HOURS

Diluent: Water for Injections BP

Drug combination	Maximum dose (mg) known to be stable in:						Comments
	8 ml in a 10 ml syringe		14 ml in a 20 ml syringe		17 ml in a 30 ml syringe		
Diamorphine and Cyclizine [149]	160 160*	If diamorphine dose >160 cyclizine dose must be no more than 80	280 280*	If diamorphine dose >280 cyclizine dose must be no more than 140	340 340*	If diamorphine dose >340 cyclizine dose must be no more than 170	*If exceed these doses then likely to get precipitate* **Maximum recommended daily dose 150 mg*
Diamorphine and Dexamethasone [209, 210]	400 3.2		700 5.6		850 6.8		*Can precipitate if undiluted drugs are mixed during preparation*
Diamorphine and Haloperidol[149]	800 24	400 32	- -		-		*If exceed these doses then likely to get precipitate*
Diamorphine and Hyoscine HBr[211]	1200 3.2		-		-		-
Diamorphine and Hyoscine Butylbromide (Buscopan)[211]	1200 160		-		-		-
Diamorphine and Ketorolac[212]	47 40		82 74		90 90		-
Diamorphine and Methotrimeprazine (Nozinan)[213]	400 80		700 140		850 170		*Mixture can be irritant, dilute to largest possible volume*
Diamorphine and Metoclopramide[211]	1200 40		2100 70		2550 85		*Mixture can be irritant, dilute to largest possible volume*
Diamorphine and Midazolam [209]	400 16		700 28		850 34		-
Diamorphine and Octreotide[214]	200 0.9		350 1.6		425 1.9		-
Diamorphine and Ondansetron[215]	40 5		70 9		85 11		

THREE DRUG COMBINATIONS FOR SUBCUTANEOUS INFUSION WHICH ARE STABLE FOR 24 HOURS

Diluent: Water for Injections BP

Drug combination	**Maximum dose (mg) known to be stable in:**			*Comments*
	8 ml in a 10 ml syringe	**14 ml in a 20 ml syringe**	**17 ml in a 30 ml syringe**	
Diamorphine **and** **Cyclizine** **and** **Haloperidol**[149]	160 160 16	280 280 28	340 340 34	*Above these doses the mixture is likely to precipitate*
Diamorphine **and** **Dexamethasone** **and** **Haloperidol**[209]	400 3.2 8	700 5.6 14	850 6.8 17	*Only stable if diamorphine and haloperidol are well diluted before dexamethasone is added.* ***Use only if no other options.***
Diamorphine **and** **Haloperidol** **and** **Metoclopramide**[213]	400 3.2 24	700 5.6 42	850 6.8 51	-
Diamorphine **and** **Haloperidol** **and** **Midazolam**[216]	560 4 32	980 7 56	1190 8.5 68	-
Diamorphine **and** **Hyoscine Butylbromide** (Buscopan) **and** **Midazolam**[216]	560 4 22	980 7 39	1190 8.5 48	*Hyoscine butybromide is usually used at doses of 60-120 mg. Stability data at these concentrations is not known in three drug combinations*
Diamorphine **and** **Methotrimeprazine** **and** **Metoclopramide**[209]	400 80 24	700 140 42	850 170 51	-

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SIGN

Control of pain in patients with cancer

Quick Reference Guide

PRINCIPLES OF MANAGEMENT OF PAIN IN PATIENTS WITH CANCER

A	Patients should be given information and instruction about pain and pain management and be encouraged to take an active role in their pain management.
B	The principles of treatment outlined in the WHO Cancer Pain Relief programme should be followed when treating pain in patients with cancer.
B	For appropriate use of the WHO analgesic ladder, analgesics should be selected depending upon initial assessment and the dose titrated as a result of ongoing regular reassessment of response.
B	A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain.
B	If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency.
B	All patients with moderate to severe cancer pain, regardless of aetiology, should receive a trial of opioid analgesia.
B	Analgesia for continuous pain should be prescribed on a regular basis, not 'as required'.

EDUCATION

B	Pre-registration curricula for health care professionals should place greater emphasis on pain management education.
B	Continuing pain management education programmes should be available to all health care professionals caring for patients with cancer.

ASSESSMENT

B	Prior to treatment an accurate assessment should be performed to determine the type and severity of pain, and its effect on the patient.
B	The patient should be the prime assessor of his or her pain.
C	For effective pain control the physical, functional, psychosocial, and spiritual dimensions should be assessed.
B	A simple formal assessment tool should be used in the ongoing assessment of pain.
B	All health care professionals involved in cancer care should be educated and trained in assessing pain as well as in the principles of its control.
C	Sudden severe pain should be recognised as a medical emergency and patients should be seen and assessed without delay.

Types of pain:

- *Somatic*
- *Visceral*
- *Neuropathic*
- *Sympathetically mediated*
- *Mixed*
- *Anguish*

PSYCHOSOCIAL ISSUES

B	A thorough assessment of the patient's psychological and social state should be carried out. This should include assessment of anxiety and, in particular, depression, as well as the patient's beliefs about pain.

KEY A B C indicates grade of recommendation ☑ Good practice point

Scottish Cancer Therapy Network

CHOICE OF ANALGESIA FOR CANCER PAIN

THE WHO ANALGESIC LADDER

STEP 3: MODERATE TO SEVERE PAIN

(opioid for moderate to severe pain plus a non-opioid ± adjuvant)

Drug options
first line
– *morphine*
– *diamorphine*
\+ *step 1 non-opioids*

alternative
– *fentanyl*
– *hydromorphone*
– *methadone*
– *oxycodone*
– *phenazocine*
+ *step 1 non-opioids*

Freedom from cancer pain

B	Morphine or diamorphine should be used to treat moderate to severe pain in patients with cancer.
C	The oral route is the recommended route of administration and should be used where possible.
B	A trial of alternative opioids should be considered for moderate to severe pain where dose titration is limited by side effects of morphine/diamorphine.

Pain persisting or increasing

STEP 2: MILD TO MODERATE PAIN

(opioid for mild to moderate pain plus a non-opioid ± adjuvant)

Drug options
– *codeine*
– *dihydrocodeine*
– *dextro-propoxyphene*
\+ *step 1 non-opioids*

B	Patients with mild to moderate pain should receive codeine, dihydrocodeine or dextropropoxyphene plus paracetamol or a NSAID.
C	If the effect of an opioid for mild to moderate pain at optimum dose is not adequate, do not change to another opioid for mild to moderate pain. Move to step 3 of the analgesic ladder.
C	Compound analgesics containing subtherapeutic doses of opioids for mild to moderate pain should not be used for pain control in patients with cancer.

Pain persisting or increasing

STEP 1: MILD PAIN

(non-opioids ± adjuvant)

Drug options
– *paracetamol*
– *aspirin*
– *non-steroidal anti-inflammatory drugs (NSAIDs)*

A	Patients with mild pain should receive either a NSAID or paracetamol at licensed doses. The choice should be based on a risk/benefit analysis for each individual patient.
A	Patients receiving a NSAID who are at risk of gastrointestinal side effects* should be prescribed misoprostol 200 μg two or three times a day or omeprazole 20 mg once a day.

Pain

* *includes patients aged>60 years, smokers, previous peptic ulcer, those on steroids or anticoagulants, patients with existing renal or hepatic disease, or cardiac failure*

USE OF OPIOIDS IN TREATMENT OF MODERATE TO SEVERE CANCER PAIN

INITIATING AND TITRATING ORAL MORPHINE

C	When initiating normal release morphine, start with 5-10 mg orally at four hourly intervals, unless there are contraindications.
B	The opioid dose for each patient should be titrated to achieve maximum analgesia and minimum side effects for that patient.
C	Where possible, titration should be carried out with a normal release morphine preparation.
A	Once suitable pain control is achieved by the use of normal release morphine conversion to the same total daily dose of controlled release morphine should be considered.

BREAKTHROUGH ANALGESIA

C	Every patient on opioids for moderate to severe pain should have access to breakthrough analgesia, usually in the form of normal release morphine.
C	Breakthrough analgesia should be one sixth of the total regular daily dose of oral morphine.
☑	Following the delivery of oral breakthrough analgesia wait 30 minutes to assess the response. If pain persists, repeat analgesia and reassess in a further 30 minutes. If pain still persists, full reassessment of the patient is required.
☑	Careful explanation of the correct use of breakthrough analgesia to carers and patients is necessary.

PREDICTABLE SIDE EFFECTS

B	**Constipation:** Patients receiving an opioid must have access to regular prophylactic laxatives. A combination of stimulant and softening laxative will be required.
☑	**Nausea and vomiting:** Patients commencing an opioid for moderate to severe pain should have access to a prophylactic antiemetic to be taken if required.
☑	**Sedation:** Patients receiving opioids for moderate to severe pain for the first time should be warned that sedation may occur and be advised of the risks of driving or using machinery. The use of other sedative drugs or drugs with sedative side effects should be rationalised.
☑	**Dry mouth:** All patients should be educated on the need for, and methods to achieve, good oral hygiene.
B	Alternative opioids can be tried in patients with opioid sensitive pain who are unable to tolerate morphine side effects.

OPIOID TOXICITY, TOLERANCE, AND DEPENDENCE

C	Opioid toxicity should be managed by reducing the dose of opioid, ensuring adequate hydration and treating the agitation/confusion with haloperidol 1.5-3 mg orally or subcutaneously. This dose can be repeated hourly in the acute situation.
B	Initiation of opioid analgesia should not be delayed by anxiety over pharmacological tolerance as in clinical practice this does not occur.
C	Initiation of opioids should not be delayed due to unfounded fears concerning psychological dependence.
B	Patients should be reassured that they will not become psychologically dependent on their opioid analgesia.

PARENTERAL ADMINISTRATION

B	Patients requiring parenteral opioids should receive the appropriate dose of diamorphine via the subcutaneous route.
C	To calculate the 24 hour dose of subcutaneous diamorphine divide the total 24 hour oral dose of morphine by 3. Administer this dose of diamorphine subcutaneously over 24 hours.
C	Safe systems for use and management of syringe drivers must be in place as detailed in guidance issued by the Scottish Executive Department of Health.

ADJUVANT ANALGESICS

A	Patients with neuropathic pain should have a trial of a tricyclic antidepressant and/or an anticonvulsant.
C	A therapeutic trial of oral high dose dexmethasone should be considered for raised intracranial pressure, severe bone pain, nerve infiltration or compression, pressure due to soft tissue swelling or infiltration, spinal cord compression, or hepatic capsular pain (unless there are contraindications). In some clinical situations (e.g. if the patient is vomiting) it may be necessary to use the intravenous route.
A	Mexiletine should not be used routinely as an adjuvant analgesic.

SYSTEMIC ANTI-CANCER THERAPY

A	In patients with metastatic breast cancer who have progressive disease despite prior tamoxifen, the use of specific aromatase inhibitors such as anastrazole and letrazole should be considered.
C	Primary endocrine therapy should be considered for all patients presenting with prostatic carcinoma and painful bone metastases.
C	Maximum androgen blockade should be considered for management of patients with prostate cancer with worsening bone pain or progression on current single agent endocrine therapy.

RADIOTHERAPY

C	Radiotherapy should be considered for painful bone metastases.
C	The management of mechanical bone pain is more complex and if the patient is fit enough should involve consultation with an orthopaedic surgeon.
B	Radioactive strontium should be considered for the management of pain due to widespread bone metastases from prostatic carcinoma.
☑	Urgent treatment should be given for all patients with spinal cord compression.

BISPHOSPHONATES

A	Bisphosphonate treatment should be considered for all patients with multiple myeloma.
A	Bisphosphonates should be considered in the management of breast cancer patients who have pain due to metastatic bone disease.

INTERVENTIONAL TECHNIQUES

A	In patients with upper abdominal pain, especially secondary to pancreatic cancer, coeliac plexus block should be considered.
C	All professionals looking after patients with pain from cancer should have access to a specialist pain relief service.

Derived from the national clinical guideline recommended for use in Scotland by the Scottish Intercollegiate Guidelines Network (SIGN)

Royal College of Physicians, 9 Queen Street, Edinburgh EH2 1JQ

Available on the SIGN website: www.sign.ac.uk

This guideline was issued in June 2000 and will be reviewed in 2002

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