SIGN

Scottish Intercollegiate Guidelines Network

NHS Quality Improvement Scotland

106

Control of pain in adults with cancer

A national clinical guideline

November 2008

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

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

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

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

SIGN 44	Verbatim extract from SIGN 44 published in 2000. This material covers areas that were not updated in the current version of the guideline.

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Pain associated with cancer increases with progression of the disease. Around a third of patients with cancer report pain, rising to three quarters in the advanced stages of cancer.[1] Attempts to control pain and hence improve functional ability and quality of life have been overshadowed in the past by attempts to cure the underlying disease.[2] Cancer pain has many dimensions including psychological, physical, social and spiritual which must be addressed in order to improve quality of life and functional ability *(see section 4.1)*.

Surveys of the effectiveness of pain control in patients with cancer reveal a varied picture. In one prospective study of more than 2,000 patients over 10 years, good or satisfactory pain control was achieved in 88%.[3] However, evidence of poor pain control also exists. In one multicentre survey of analgesic drug therapy for cancer pain in France 51% of patients reported inadequate pain relief following treatment.[4,]

A quantitative and qualitative study of pain relief in Italy reported inadequate analgesia in 43% of patients.[5] Discrepancies in the proportion of patients reported to achieve adequate analgesia may be related to a lack of standardisation of assessment and treatment although other patient-dependent factors may be involved.

Access to comprehensive, contemporary evidence based guidelines supports health professionals in their aim of relieving patients' distress.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of pain in adult patients who have cancer. The guideline includes advice mainly concerning pain secondary to the cancer, but many of the principles outlined are applicable to coexisting painful conditions and pain secondary to treatment of the cancer. It excludes the treatment of pain in children under the age of 12.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to any health professional likely to encounter a patient with cancer-related pain of any severity, including palliative care staff, physicians, surgeons, anaesthetists, nurses, physiotherapists, occupational therapists, interventional radiologists, oncologists, nurses, pharmacists, clinical psychologists, general practitioners and spiritual and religious care providers. It will also be of interest to patients with cancer pain and their carers.

1.3 DEFINITIONS

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."[6]
- "pain is a category of complex experiences, not a single sensation produced by a single stimulus."[7]
- "pain is what the experiencing person says it is, existing whenever (s)he says it does."[8]

For the purposes of this guideline, the first of these definitions is used.

Breakthrough pain is pain of moderate or severe intensity arising on a background of controlled chronic pain. Breakthrough pain may be described as spontaneous (unexpected) or incident (expected or predictable).[9]

Spiritual care is usually delivered in a one to one relationship, is completely person centred and makes no assumptions about personal conviction or life orientation. It may be provided by all health care staff, by carers, families and fellow patients.[10]

Religious care is provided in the context of shared religious beliefs, values, liturgies and lifestyle of a faith community. Chaplains are the main providers of religious care.[10]

Psychological distress has been defined by the National Comprehensive Cancer Network as "..a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional) social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common, normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, social isolation, and existential and spiritual crisis".[11] 4

Throughout this guideline **opioid medications** will be classified as per custom into weak and strong opioids. Examples of weak opioids are codeine, dihydrocodeine and tramadol. Examples of strong opioids are morphine, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine and methadone. Weak opioids generally are used for treating mild to moderate pain and strong opioids for moderate to severe pain.

Adjuvant analgesics are drugs with other primary indications that can be effective analgesics in specific circumstances.[12] 4

1.4 LICENSING OF DRUGS IN PALLIATIVE CARE

In palliative care, up to a quarter of all prescriptions written are for licensed drugs given for unlicensed indications, and/or via an unlicensed route. Often it is simply a matter of the route or dose being different from those in the manufacturer's Summary of Product Characteristics. Prescribing, dispensing and administration of drugs outwith licence is often appropriate in palliative care and may represent standard practice.[13] In this guideline, recommendations which include the use of licensed drugs outwith the terms of the licence reflect the evidence base which was reviewed. 4

1.5 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of 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. Adherence to guideline recommendations 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 must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.5.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, **www.sign.ac.uk**

1.5.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section on implementation.

2 Patient issues

2.1 NARRATIVE REVIEW OF PUBLICATIONS DESCRIBING PATIENT ISSUES

A narrative review of the qualitative literature was conducted to identify issues of concern to patients with cancer pain. The search strategy is outlined in section 11.1.2.

The narrative review identified three main issues that arose either from incidental findings from other research or as primary topics in their own right. These were:

- communication (between patients/carers and healthcare professionals, among healthcare professionals, among patients/carers)
- spirituality and coming to terms with living with a serious illness
- the impact of cancer pain on relationships.

These topics are not discrete, they overlap and are inter-related. For example, one study highlights the communication implications of existential crisis.[14] These topics reflect the most frequently cited issues and are not a comprehensive list of insights generated by qualitative researchers.

Much of the literature identified was limited by the methodological quality of the studies (*see supplementary material on SIGN website for further details of the methodological analyses undertaken*).

2.2 COMMUNICATION

2.2.1 COMMUNICATION BETWEEN PATIENTS/CARERS AND HEALTHCARE PROFESSIONALS

For patients, good communication, planning and trust are fundamental concepts for perceived control of cancer-related pain. To achieve patients' wishes for maximum pain relief with minimal side effects pain should be assessed and discussed early in the patient's course of the disease (before reaching the palliative stages).[15] When appropriate, patients should be told that most pain can be relieved by medication without persistent side effects. Fears about use of medication should be addressed. Communication is enhanced when information is presented in an accessible way and patients experience a sense of confidence, trust, and being listened to.[16,17]

Good encounters with professionals can lead to better patient concordance with therapy and better adjustment to diagnosis.[16]

Carers can play an active role in assessment and management of pain but carer managed analgesia requires good communication with the clinician. Clinicians should be aware of the burdens realised on the carers of patients with cancer pain.[18]

Clinicians and nursing staff should get to know the patient and family as well as possible so as to enable patients and family to voice their fears, wishes and concerns with confidence.

Patient input plays a major part in getting the most out of treatment. Clinicians should encourage patients to report intensity, quality, location and pattern of pain. Patients found diaries useful for managing their own self care and reporting their symptoms but these were best used when there was some initial training input by a health professional.[19]

A study with methodological limitations described how the fears generated by a diagnosis of primary stage head and neck cancer led to an under-reporting of experiences.[14] Addressing existential concerns can be an aid to communication. A further study found under-reporting of pain in men and women with metastatic bone pain led to avoidable under-treatment.[20] Whether or not pain was communicated was influenced by, and had an influence on, relationships between patient and healthcare professional.

The limitations of quantitative measures of pain were highlighted in a paper which suggested that the meaning of symptoms influenced patients' reports of pain.[21] Most communication between patients and professionals is provider driven, which would mitigate against tapping into the existential experience.[22] Provider directed communication may focus on the physical domain alone.[23]

Communication among healthcare professionals

Clinicians at all levels must communicate fully with each other and with nursing and care staff, the patients and their families and carers. As the community is increasingly the site of care, general practitioners (GPs) and community nursing staff should be fully involved.[24]

Communication among patients/carers

Patients find it easier to communicate with others who have had similar experiences, than others who have not. This helps to create an understanding of what is happening to them. Having developed this shared understanding they are better able to communicate with healthcare professionals.[25,26]

2.2.2 KEY MESSAGES

- Good communication with patients and carers happens when:
  - it is at their level of understanding;
  - is non-patronising;
  - free of jargon;
  - healthcare staff know the patient and carers well and actively listen.
- Poor communication between patients and professionals may result in clinical assessment that is not comprehensive, and under-reporting of pain by patients.
- Pain, its assessment and management should be discussed at an early stage of the disease.
- Patients find it easier to talk about their pain when given strategies that enable them to do so: this may include diaries, and the opportunity to talk to other patients.

☑ Cancer services should facilitate peer support to enable patients to communicate effectively with professionals and others.

☑ Healthcare professionals should be given training to overcome the specific challenges around communication with people with cancer, their carers and other professionals.

2.3 SPIRITUALITY, SUBJECTIVE EXPERIENCE AND MEANING MAKING

A series of studies explored how patients try to make sense of their experience of pain and to come to terms with a life threatening illness, in the context of their belief system (including specific faith based frameworks).

Other studies have dealt with cancer and pain and its impact on how people see themselves, their experiences, and place in the world. One study of elderly hospice patients found that psychological and social pain were identified as worse than physical pain and concluded that professionals should be educated about this type of pain.[27] Patients reported that talking to others helps to provide a cognitive map and language to aid communication.[26] Another study described the problems associated with meaning making in the context of spiritual pain and the lack of a language for dealing with this. It suggests that patients require a strong connection with life (or spirituality) in order to cope with aggressive and invasive cancer treatments and the development of a suitable language to express notions of spiritual pain may reduce patient frustration and enhance communication.[25]

There is some qualitative evidence that, in addition to conventional treatments, strengthening religious faith is important in fostering the ability of some terminally ill patients to cope.[27]

2.3.1 KEY MESSAGES

- Cancer can destabilise patients' lives in terms of their self identity, belief systems and place in the world.
- Individuals need a sense of meaning to life and of making a connection with life to be able to deal with the demands of aggressive or invasive treatments.
- Patients experience the 'existential challenge' of cancer as a kind of pain that can be greater than physical pain.
- Patients value professionals who adopt a holistic approach to care and are competent in dealing with (and are able to communicate about) the spiritual, psychological, and emotional impact of pain.

☑ Healthcare professionals should be educated about the psychological and social dimensions of the cancer experience.

☑ Service providers and those providing education should have a basic understanding of the range of beliefs held by patients across a multifaith and multicultural context.

☑ Support should be provided for professionals in dealing with the impact of their work on their own understanding of themselves and their belief systems.

2.4 RELATIONSHIPS

Cancer pain is not always as well managed as it could be, highlighting the need for ongoing training in pain management for healthcare professionals. A key feature of this training relates to the team approach required for good cancer care and pain management.[5,17,28]

Lack of adequate pain control is a persistent problem frequently reported by patients. There is little evidence that patient education without support is effective in improving pain control. A systematic multidisciplinary approach is required, a team effort in which patient, carer, clinician, nurse, pharmacist and other support staff interact. This implies a need to improve healthcare providers' relationship-building skills, improve coordination among providers and involve carers.[17,29]

Dying patients need emotional support from accessible professionals with good communication skills. This requires an ability to acknowledge and empathise with and get to know the patient, balance reality with positivity, treat the whole person, and be prepared to discuss every aspect of the patient's life affected by their cancer, if the patient so wishes.[30]

2.4.1 KEY MESSAGES

Effective interprofessional teamwork is required for good cancer pain management.

☑ Training is required to ensure effective interprofessional communication and teamwork.

3 Psychosocial issues

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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.[31] 4

Psychological factors can have a profound influence on the perception of pain and how the sufferer responds behaviourally and emotionally. As a chronic stressor, chronic pain can give rise to disability and distress, but this can be mediated by psychological factors. There is a large body of scientific evidence to support the role of anxiety and depression, fear, particular pain-related beliefs and coping styles in the mediation of pain perception in chronic non-malignant pain. Cognitive behavioural interventions designed to minimise the impact of pain on mood and function are effective in this patient group.[32] 1^{++}

The meaning of pain may be different for patients with cancer compared to those patients with pain relating to non-life threatening illness. Some cancer patients may see increased pain as a sign of disease progression or the failure of strong medication, with possible consequences for mood and adherence to treatment protocols. There is emerging evidence that education and cognitive behavioral interventions for cancer pain can alleviate some of the distress and disability associated with pain, as well as improving adherence to analgesic regimens.[33,34] 1^{++} 1^{+}

3.1 PSYCHOLOGICAL DISTRESS

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The prevalence of depressive disorders of all types is significantly higher in those patients with cancer with high levels of pain than in patients with lower levels of pain, even when patients with more severe pain have a significantly lower previous history of depression. This may suggest that not only are pain and psychiatric morbidity correlated but that cancer pain may play a role in producing or exacerbating depression.[35] A diagnosis of depression is often missed in patients with cancer.[36] There is an overlap between symptoms of depression, symptoms of cancer, and the effects of cancer treatments.[35] Careful and extensive questioning can elucidate the extent to which the symptom relates to emotional distress, to the cancer or to the treatment. 3 4

3.1.1 PREDICTING PSYCHOLOGICAL DISTRESS

One systematic review, which included 31 papers, identified a strong association between psychological distress and cancer pain.[37] There was also a significant association found between lack of social support and cancer pain. There is limited evidence for an association between coping style and cancer pain, with the exception of catastrophising. 2^{++}

Catastrophising is a thought process characterised by an excessive focus on pain sensations (rumination, "I can't stop thinking about how much it hurts") with an exaggeration of threat (magnification, "something serious might happen") and the self-perception of not being able to cope with the pain situation (helplessness, "there is nothing I can do to reduce the pain").[38] 3

A UK study, using qualitative methods, showed a link between catastrophising and expected pain levels in the future. Overestimates of future pain have a negative effect on mood.[39]

These findings are consistent with the literature on non-cancer chronic pain.[40] 4

B **Comprehensive chronic pain assessment should include routine screening for psychological distress.**

☑ Screening for psychological distress should be carried out using a validated tool.

3.1.2 MANAGING PSYCHOLOGICAL DISTRESS

There is strong evidence to support the efficacy of cognitive behaviour therapy (CBT) interventions in the management of chronic, non-malignant pain when delivered by qualified professionals.[32] There is also evidence to suggest that some CBT techniques can improve quality of life and reduce distress on those with cancer-related pain. A meta-analysis of randomised controlled trials (RCTs) involving 3,216 patients with cancer showed components of CBT led to improvements in depression, social outcomes, objective physical outcomes, and quality of life.[33] 1++

A meta-analysis of 20 studies looking at the effect of CBT techniques in a total of 2,133 breast cancer patients showed that 62% of patients did better with regards to distress, while 69% did better with regard to pain levels. Individual therapy had a better outcome for distress than group formats.[41] 1++

In an RCT using a partner guided cognitive behaviour intervention, partners of cancer patients demonstrated improved self efficacy in helping patients control pain and other symptoms.[42] 1+

A systematic review of pharmacological and psychotherapeutic interventions for depression in cancer found limited evidence for the use of either intervention. This review identified a number of small scale studies which showed an effect of CBT on depressive symptoms in cancer patients however these lacked control for possible confounding factors and it was not possible to draw firm recommendations from this evidence.[34] 1+

One RCT showed a negative impact of pain on the response of depression to treatment.[43] Patients were randomised to receive either a collaborative care intervention or usual care in primary care. Both baseline pain and the amount of pain improvement over time were associated with depression remission and response rates. In a multivariate model controlling for age, gender, and medical comorbidity, depression severity increased with higher pain interference and decreased with the passage of time ($p < 0.0001$ for both). 1+

A **Cognitive behaviour therapy should be considered as part of a comprehensive treatment programme for those with cancer related pain and resulting distress and disability.**

3.2 PSYCHOLOGICAL FACTORS AND ADHERENCE TO TREATMENT

Twenty eight to 38% of all cancer pain patients do not comply with their analgesic regimens.[44] A biopsychosocial approach to pain management recognises the role of idiosyncratic patient thoughts and beliefs in influencing the behavioural response to such pain. Such beliefs can form as a result of past experience of pain, family influences, and contact with healthcare professionals. Examples of such beliefs might include perceived lack of control over pain, that pain increase is a sign of disease progression, and that analgesic medication may lead to addiction. 1+

One single cohort study involving 194 Taiwanese cancer patients showed that patients who have a stronger belief in the role of medication to control pain, and weaker beliefs in their own ability to control pain, were significantly more likely to adhere to medication. This study suggests that pain beliefs should be assessed and integrated into pain management and patient education to enhance adherence.[45] 3

Other qualitative studies with western populations also suggest a link between patient beliefs and adherence to medication.[46,47]

D **Patient beliefs concerning pain should be assessed and discussed as part of a comprehensive, biopsychosocial cancer pain assessment.**

3.2.1 EDUCATIONAL INTERVENTIONS

A review of methods of disseminating educational interventions found no specific intervention to be effective in changing patient beliefs or behaviour in cancer pain. Advice from healthcare professionals, removal of financial barriers and multicomponent interventions were effective in changing patient beliefs in non-cancer pain settings. For healthcare professionals, role modelling and workshops did increase dissemination of information but the effects were small and did not change behaviour.[48] 2+

A further study showed improvement in nurse knowledge following an educational intervention. The study did not examine the impact of this knowledge on nurse behaviour.[49] 1+

A meta–analysis showed that relaxation-based cognitive behaviour interventions, education about analgesic use and supportive counselling reduced pain scores in conjunction with analgesic use.[50] 2++

Two RCTs carried out in Taiwan found that educational interventions can change patients' cancer pain related beliefs and behaviour. In the first, the 18 patients who received pain education showed significant reductions in strength of beliefs relating to non-adherence to analgesic medication, as measured by the Barriers Questionnaire, and showed improvements in medication adherence when compared to the 19 patients in the control group.[51] In the second study following a pain management education programme for patient and carer pairs, significantly lowered scores on the Barriers Questionnaire, and improved adherence to analgesic medication.[52] 1+

Receiving a psychoeducational intervention has also been shown to reduce the reporting of pain compared with those receiving standard care.[53] 1+

C **Patients should receive education about the range of pain control interventions available to them.**

4 Assessment of pain

4.1 WHAT IS PAIN?

Pain is more than a physical phenomenon although the psychological, social and spiritual aspects of pain are not always considered.

Research suggests that a multidimensional approach to pain assessment and a linkage between physically expressed pain, psychological state, social and spiritual issues are integral to a person's reaction to their pain experience.[54] A comprehensive assessment of pain should consider the following domains:

- physical effects/manifestations of pain[55]
- functional effects (interference with activities of daily living)[56]
- psychosocial factors (level of anxiety, mood, cultural influences, fears, effects on interpersonal relationships, factors affecting pain tolerance; *see Table 1*).[57,58]
- spiritual aspects.

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3
4

Table 1: Factors affecting pain tolerance (adapted from Twycross and Lack)[59]

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	Social inclusion
Mental isolation	Encouragement to express emotions

4.1.1 SPIRITUAL ASPECTS OF PAIN

Spirituality relates to ideas of meaning of purpose and of the continuity of life. It does not always include a religious component.[60,61] Atheists may have spiritual needs. A meaningful spiritual assessment understands that there is no clear definition of 'spiritual needs'. It requires a person centred approach.[62] Spiritual pain is the result of the experience of illness and facing death which may cause a patient to struggle with existential (why) questions, lose their sense of meaning and purpose in life and feel isolated in doing so.

4

Chaplains and some 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 (*see section 2.3*).

4.2 WHY ASSESS PAIN?

Uncontrolled pain limits a person's ability to self care, affects their response to illness and reduces their quality of life.[63] Accurate assessment and diagnosis of the likely neural pathways involved, type of pain, its severity, and its effect on the person are essential to plan appropriate interventions or treatments, and are an integral part of overall clinical assessment.[64-69] The aetiology of the pain should also be considered as it cannot always be attributed to the underlying cancer. Five to ten per cent of patients with malignant disease report pain due to other conditions.[70]

3
4

Careful history taking *(see section 4.4.1)* and listening attentively to the patient will usually diagnose the type of pain and this in turn dictates the therapy. The severity of the pain will determine the step of the World Health Organization (WHO) ladder *(see section 5.2.1)* at which the therapeutic intervention will begin.

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

4.3 WHO SHOULD ASSESS PAIN?

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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.[71,72] Family members tend to overestimate pain in their relatives.[73] 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.[74]

3

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

Due to frailty, cognitive impairment or communication deficits not all patients are able to relate the story of their pain. Completion of pain scoring tools may not be possible. In these cases families or health professionals may act as a surrogate *(see section 4.4.3)*.[71]

4.4 HOW SHOULD PAIN BE ASSESSED?

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

4.4.1 CLINICAL HISTORY AND PHYSICAL EXAMINATION

Detailed history taking is vital to comprehensive assessment. The guideline development group suggests that history taking should include:

- 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 (eg decubitus ulcers)
  - pain unrelated to cancer or treatment
- type of pain
  - nociceptive
  - visceral
  - neuropathic
  - complex regional pain syndrome.
  - mixed
- analgesic drug history
- patient beliefs about the meaning of pain, effectiveness of its treatments and consequences of drug therapies *(see section 3.2)*
- presence of clinically significant psychological disorder eg anxiety and/or depression.

4.4.2 PAIN ASSESSMENT TOOLS

Many different pain assessment tools are used throughout the world, which leads to difficulties in comparing the results of analgesic management.[75] There is no universally accepted tool for the assessment of cancer pain. Careful selection of a comparable and transferable pain assessment tool is required to allow valid comparisons between future studies.

In a subgroup analysis of data from an RCT of 313 cancer patients with pain of at least one month's duration pain parameters were measured at baseline and then two, four and eight weeks after discharge from hospital using four different pain assessment tools.[76] The tools used were pain intensity markers (an 11-point numeric rating scale that rated patients' present pain intensity, average pain intensity during the last week, and worst pain intensity); a pain relief scale; a patient satisfaction scale and a set of pain management indices. The percentage of patients identified as having poor pain control varied (16%-91%) according to which tool was used. When worst pain was measured, approximately nine out of every 10 patients were assessed as receiving inadequate pain treatment; in contrast, use of the pain relief scale resulted in fewer than two out of every 10 patients being scored as treated inadequately. This demonstrates the degree of inconsistency between these tools. | 1+

To overcome this problem the European Association of Palliative Care recommended the use of standardised pain assessment tools in palliative care both in research and in clinical practice. These include visual analogue scales (VAS), numerical rating scales (NRS) and verbal rating scales (VRS).[77] | 4

Visual analogue scales, NRS and VRS are valid tools for measuring pain in the cognitively impaired, very elderly, or patients in the dying phase (*see section 4.4.3*).[78,79] | 3

The McGill Pain Questionnaire and the Brief Pain Inventory are multidimensional pain assessment questionnaires that incorporate NRS and VRS and have been validated in different cultures.[80,81] | 3

One single-cohort study investigated the inter-rater reliability and predictive validity of the revised Edmonton Staging System (rESS) as a tool for classifying cancer pain.[82] Results indicated that age (for age >60 years, hazard ratio HR 1.64, 95% confidence interval CI 1.29 to 2.07), the presence of neuropathic pain (HR 0.46, 95% CI 0.35 to 0.62), incident pain (HR 0.60, 95% CI 0.47 to 0.75), psychological distress alone (HR 0.70, 95% CI 0.53 to 0.92), or comorbid psychological distress/addiction (HR 0.55, 95% CI 0.31 to 0.99) all classified by rESS were significantly associated with increased time to achieve stable pain control. Patients with neuropathic and incident pain required significantly more adjuvant management options to achieve stable pain control than patients with other pain features ($p < 0.001$). 3

A study of 111 cancer patients examined the relationship between pain intensity and emotional experience.[54] In men the strongest correlations were found between pain and anger and frustration (0.64), anger and fear (0.50) and hopelessness and helplessness (0.50). In women, hopelessness and helplessness (0.76) helplessness and anger (0.65) and hopelessness and fear (0.59) were most strongly correlated to physical pain. It was not possible to determine whether the emotional response was a consequence of the pain or contributed to the level of pain intensity. 3

D **Patients with cancer pain should have treatment outcomes monitored regularly using visual analogue scales, numerical rating scales or verbal rating scales.**

4.4.3 PAIN ASSESSMENT IN PATIENTS WITH COGNITIVE IMPAIRMENT

The presence of cognitive impairment makes pain assessment more difficult. The level of impairment is influential. Most studies are in patients suffering from dementia. A prospective study of four self assessment scales in 160 patients in a geriatric hospital found that only 12% could not understand any of the four self assessment scales used.[83] These were the verbal rating scale (none, mild, moderate, severe), the horizontal visual, vertical visual and faces pain scales. Respectively 97%, 90% and 40% of patients with mild, moderate, and severe dementia understood at least one scale ($p < 0.05$). 2^+

A systematic review of behavioural pain assessment tools for elderly people with severe dementia concluded that the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) and DOLOPLUS2 are the most appropriate scales for this group.[84] Neither scored more than 12 out of a maximum of 20 points for quality and their overall psychometric quality is moderate. It is not clear if the English language version of DOLOPLUS2 has been psychometrically tested. In acute settings, the value of this test may be limited because patients must be well known to the nurse who completes the tool. The value of a scale becomes greater if it can be used without in depth knowledge of the patient.[85] 2^{++} 3

C

- **Self assessment pain scales should be used in patients with cognitive impairment, where feasible.**
- **Observational pain rating scales should be used in patients who cannot complete a self assessment scale.**

4.4.3 FREQUENCY OF ASSESSMENT

One of the keys to successful control of cancer pain is regular review to determine the effectiveness of treatment. The frequency of the review depends upon the severity of the pain and associated distress. One observational study showed that 74% of patients were satisfied with twice daily pain assessment. Nurses agreed that daily pain assessment was important and feasible in this study.[86]

☑ Pain assessment should be carried out regularly (at least daily when pain is not adequately controlled).

5 Principles of pain management

5.1 INTRODUCTION

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

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Involvement of patients in their treatment improves pain control. A study of the effectiveness of a pain management intervention in 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.[87] Information and an explanation about their medication will form part of this. 1+

B **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 WORLD HEALTH ORGANIZATION CANCER PAIN RELIEF PROGRAMME

In the mid 1980s the World Health Organization launched a cancer pain programme which recommended a logical approach to pain control.[88] The WHO analgesic ladder has gained worldwide acceptance (*see figure 1*). 4

5.2.1 PRINCIPLES OF THE WORLD HEALTH ORGANIZATION CANCER PAIN RELIEF PROGRAMME

The principles of the WHO cancer relief programme are that:

- detailed multidimensional assessment of severity of pain is essential
- the patient is started on the appropriate level of the ladder for the degree of pain, based upon the results of the assessment
- analgesia is given regularly dependent upon the pharmacokinetics of the chosen drug and its formulation
- medication for breakthrough pain must be prescribed 4
- laxatives are required and should be prescribed for the vast majority of patients on opioid analgesics (*see section 7.7*)
- adjuvant drugs must be considered and the class of drug chosen according to the type of pain
- paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) should be used at all steps of the ladder unless contraindicated
- the oral route of drug delivery is strongly advocated in the chronic pain usually encountered by the person with cancer.
- morphine is the strong opioid of choice.

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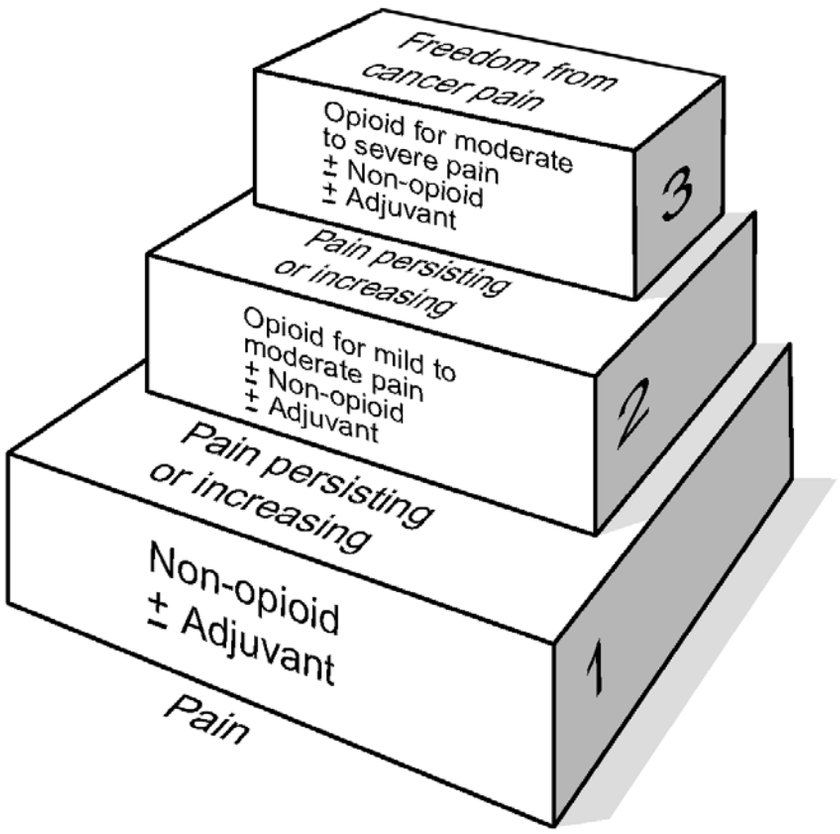
In many cases a multidisciplinary approach is required to give the optimum outcome for the patient. Professionals involved may include physicians, anaesthetists, surgeons, GPs physiotherapists, interventional radiologists, occupational therapists, oncologists, nurses, pharmacists, clinical psychologists, palliative care specialists and spiritual care advisors.

D **The principles of treatment outlined in the WHO cancer pain relief programme should be followed when treating pain in patients with cancer.**

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

Figure 1: World Health Organization analgesic ladder



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5.2.2 THE WORLD HEALTH ORGANIZATION ANALGESIC LADDER

The three-step ladder specifies treatment according to the intensity of pain. By referring to drug classes, rather than specific drugs, the ladder maintains a level of flexibility that allows clinicians to work within the regulations and limitations employed in their respective countries. The fundamental aim of the WHO ladder was to justify the prescribing of strong opioids for cancer pain, which had previously been problematic due to fears of addiction, tolerance and illegal use.[89]

The application of this analgesic regimen has been shown to achieve pain relief in the majority of patients with cancer. One retrospective report showed that using the ladder reduced pain to one third of its initial intensity in 71% of patients.[90] One long term prospective study reported that "good" pain relief was achieved in 76% of 2,118 patients treated in accordance with the WHO guidelines over a ten year period.[3] | 3

Despite the ladder's success in providing pain relief, its use and design has been debated.[91-93] | 3

Most criticism of the WHO ladder questions the usefulness of weak opioids in the treatment of cancer pain (step 2). There is insufficient evidence to either support or refute the WHO recommendation that a weak opioid has superiority over an NSAID.[94] | 1++

In those with rapidly advancing pain, or in need of rapid titration of analgesic therapy, the switch between steps 1 and 2 may delay optimal pain relief. In opioid-naïve patients a balance between side effects and analgesia has been demonstrated by administering a weak rather than a strong opioid.[95] There is also evidence to support the successful use of strong opioids in opioid-naïve patients.[96-98] | 2+

Controlled trials are required to further validate these findings.

One RCT showed that moving directly from step 1 to step 3 of the WHO analgesic ladder was possible and could reduce pain scores in some cases, but attentive management of side effects was required.[99] This has led to alternatives to the WHO ladder being proposed, usually replacing weak opioids at stage 2 with low doses of strong opioids. An RCT found equivalent analgesia with fewer drug and dose changes but higher incidence of nausea in patients omitting step 2 of the ladder.[100] 1+

The development of new formulations of opioids (eg transdermal fentanyl and buprenorphine), new routes of delivery (eg buccal fentanyl, intranasal fentanyl) and the more widespread availability of different opioids (eg oxycodone, hydromorphone) create options which were not available at the time of the development of the WHO ladder.[101] 4

5.3 USING THE WORLD HEALTH ORGANIZATION ANALGESIC LADDER

Pain relief should be based on a complete patient assessment that differentiates pain distress from pain severity *(see section 4.4.1)*. 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.[3,90] Effective use of the WHO ladder depends on accurate initial regular pain assessment and regular follow up. 4

5.3.1 SEVERITY OF PAIN

A non-systematic review of RCTs investigated the classification of pain intensity into categories and the relationship of these to the continuous scale of the VAS. Individual pain scores for each patient were assessed by a categorical scale (none, mild, moderate or severe) and by a VAS (0-100). Comparisons between the scores showed that 85% of patients scoring moderate pain had a VAS of >30 mm and 85% of patients recording severe pain had a VAS of >54 mm.[102] There was a significant difference between VAS scores for those reporting moderate or severe pain ($p<0.001$). There was no significant difference between males and females. This correlation has been found in other studies and allows transference of the patient's pain score to the analgesic ladder *(see Table 2)*.[78,79] 4

Table 2: Categorisation of pain and appropriate analgesia

WHO analgesic ladder step	Score on numerical rating scale	Analgesics of choice
1 (mild pain)	<3 out of 10	paracetamol and NSAIDs
2 (mild to moderate pain)	3 to 6 out of 10	weak opioids (eg codeine or dihydrocodeine) plus paracetamol and NSAIDs *(see section 7.1.1)*
3 (severe pain)	>6 out of 10	strong opioids (eg morphine, alfentanil, diamorphine, fentanyl, hydromorphone or oxycodone) plus paracetamol and NSAIDs *(see section 7.1.2)*

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. For chronic pain, analgesia must be given regularly by the clock. Breakthrough medication must be prescribed.

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.[103,104] 1+

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 analgesia should always be adjusted as the pain severity alters.**

☑ 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.

☑ 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 should be maintained by giving the drug at regular intervals according to its pharmacokinetic and pharmacodynamic profile.[3,90] 4

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

D **Appropriate analgesia for breakthrough pain must be prescribed.**

☑ Explain to patients with chronic cancer pain that pain control medication must be taken regularly to gain optimal results.

6 Treatment with non-opioid drugs

Non-opioid drugs may be used at any stage of the WHO analgesic ladder. Their use may result in synergistic effects when used with opioids, producing better pain relief at lower doses of opioids with potentially fewer opioid side effects.

6.1 PARACETAMOL AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Paracetamol and NSAIDs are universally accepted as part of the treatment of cancer pain.

Non-steroidal anti-inflammatory drugs are more effective than placebo for reducing cancer pain though a systematic review identified no evidence to endorse superior efficacy of one NSAID over another.[94] This systematic review reported conflicting evidence regarding the question of pain relief from combining an opioid with an NSAID compared with using either drug alone. Although the studies demonstrate that addition of an NSAID to an opioid regimen, or vice versa, increases pain relief compared to single drug, they do not necessarily demonstrate that it is this combination that is responsible for the effect. The possibility that increasing the dose of either single entity would achieve a similar outcome cannot be discounted. 1++

Conflicting results, combined with the short duration of the studies, do not allow a conclusion to be drawn on whether escalating doses of NSAIDs increase pain reduction and/or increase the incidence and severity of side effects.

It is not possible to recommend an optimal dose of NSAID for pain relief, but the Commission on Human Medicines advise that the lowest effective dose of NSAID or cyclo-oxygenase-2 (COX-2) selective inhibitor should be prescribed for the shortest period to control symptoms and that the need for long term treatment should be reviewed periodically.[105] 4

One small randomised study (n = 30) found paracetamol improved pain and well-being in patients with cancer pain already on a strong opioid regimen.[106] Further confirmation of this effect is required. 1+

A **Patients at all stages of the WHO analgesic ladder should be prescribed paracetamol and/or a non-steroidal anti-inflammatory drug unless contraindicated.**

6.1.1 REDUCING ADVERSE EFFECTS ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The most common serious adverse effects of NSAIDs are due to ulceration of the gastrointestinal (GI) tract. One systematic review examined 40 RCTs mainly in patients with osteoarthritis or inflammatory arthritis.[107] Eleven studies with 3,641 patients found the incidence of endoscopic gastric ulcers to be 15% and endoscopic duodenal ulcers to be 6% over three months. The incidence of clinically important NSAID induced ulcer complications (eg perforation, haemorrhage or obstruction) in one RCT of 8,843 patients was only 1.5% per year.[108] As many endoscopic ulcers never become clinically evident estimates such as the number needed to harm (NNH) are difficult to interpret clinically when applied to endoscopic rather than clinical end points. 1++

The following have been shown to increase the risk of upper GI toxicity when NSAIDs are prescribed:[109]

- increasing age (>65 years)
- previous peptic ulcer disease, particularly if complicated with haemorrhage or perforation
- comorbid medical illness
- smoking
- type of NSAID (eg ketoprofen, ketorolac and piroxicam are associated with a high risk of serious gastrointestinal toxicity relative to other NSAIDs)
- increasing NSAID dose
- use of multiple NSAIDs
- combined use of NSAIDs and other drugs which could increase the risk of ulceration or bleeding such as corticosteroids, anticoagulants (eg warfarin), selective serotonin-reuptake inhibitors or antiplatelet agents (eg aspirin)
- existing renal, cardiac or hepatic impairment.

4

Ibuprofen is associated with the lowest risk of GI side effects compared with other commonly used NSAIDs (eg diclofenac and naproxen). Cyclooxygenase-2 selective inhibitors (eg celecoxib, etoricoxib, lumiracoxib and parecoxib) as a class produce significantly fewer GI symptoms and clinically important ulcer complications than traditional NSAIDs although these can still cause serious, and sometimes fatal GI reactions.[110]

4

Cardiovascular risk

Randomised controlled trials have shown that COX-2 selective inhibitors demonstrate an increased risk of thrombotic cardiovascular adverse reactions, particularly myocardial infarction (MI) and stroke.[12] The excess risk is estimated to be 3 cases per 1,000 users per year. All COX-2 selective inhibitors are contraindicated for patients with established ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.

In 2006 the Commission on Human Medicines advised that there was sufficient evidence to suggest that certain traditional NSAIDs may also be associated with a small increased risk of thrombotic events when used at maximum recommended dose for long term treatment. Diclofenac 150 mg/day and ibuprofen 2,400 mg/day have a thrombotic risk profile similar to COX-2 selective inhibitors.[111] Epidemiological evidence suggests that naproxen 1,000 mg/day and ibuprofen 1,200 mg/day are not associated with an excess risk of MI.

Pharmacological prophylaxis

Misoprostol, standard dose proton pump inhibitors (PPIs) and double dose histamine-2 receptor antagonists (H2RAs), equivalent to ranitidine 300 mg twice daily, are effective at preventing chronic NSAID related gastric and duodenal ulcers.[107] Standard dose H2RAs are not effective at reducing the risk of NSAID induced gastric ulcers.

1++

Misoprostol at 800 mcg/day has been shown to reduce the risk of ulcer complications such as perforation, haemorrhage or obstruction by 40%.[108] To prevent one clinically important GI event, 260 patients would need to be treated with misoprostol though this would be lower with higher risk patients. Misoprostol even at lower doses (400 mcg/day) is associated with a higher incidence of side effects than PPIs and H2RAs. At this dose misoprostol is less effective at reducing clinical ulcer complications.

1++

There is evidence from observational studies that taking a PPI in combination with an NSAID is associated with a significant reduction in upper GI ulcers and complications compared with NSAID treatment alone.[110] There is no good evidence that a COX-2 selective inhibitor in combination with a PPI is better or worse than a traditional NSAID in combination with a PPI for preventing GI complications.[112]

4

No evidence was identified that any PPI is more effective than another.

Symptoms of dyspepsia, nausea and abdominal pain are frequently reported with the use of NSAIDs but do not correlate with the occurrence of NSAID induced ulcer complications, such as bleeding, and respond variably to the prophylactic agents.[108]

A **Patients taking non-steroidal anti-inflammatory drugs who are at high risk of gastrointestinal complications should be prescribed either misoprostol 800 mcg/day, standard dose proton pump inhibitors or double dose histamine-2 receptor antagonists as pharmacological prophylaxis.**

6.2 BISPHOSPHONATES

Two systematic reviews suggest that bisphosphonates reduce cancer pain and skeletal-related events associated with bone metastases.[113,114] The number needed to treat (NNT) to gain analgesic benefit is 11 (95% CI 6 to 36) at four weeks and 7 (95% CI 5 to 12) at 12 weeks. In comparison, the NNT for analgesic response to radiotherapy for bone metastases is 4.2.[115] 1++ 1+

Other evidence is heterogeneous as studies have not always used the same measurement tools for pain and sample sizes vary considerably. The evidence identified proved insufficient to evaluate:

- the comparative effectiveness of the different bisphosphonates for pain relief
- the analgesic response to bisphosphonates by individual primary disease site
- the optimum dose or route of administration
- the effectiveness of bisphosphonates compared with radiotherapy or other analgesics.

The main adverse effect of bisphosphonates is renal toxicity. The NNH is 16 (95% CI 12 to 27) for adverse events requiring discontinuation of bisphosphonates.[113] 1++

In one RCT, patients who had previously received either 6 mg IV ibandronate or placebo every three to four weeks for 96 weeks, then all received 6 mg IV ibandronate every three to four weeks. Six per cent in the group originally receiving placebo and 9% in the group previously receiving ibandronate experienced renal deterioration.[116] 1+

The SIGN guideline on the management of breast cancer notes that there is conflicting evidence for the effectiveness of bisphosphonates in reducing bone metastases in patients with high risk early breast cancer.[117] 4

There is insufficient evidence to recommend bisphosphonates for first line therapy.

B **Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with metastatic bone disease.**

☑
- As hypocalcaemia is a noted potential complication of administration of intravenous bisphosphonates, calcium levels should be included as part of the routine monitoring of therapy.
- Calcium and vitamin D supplements may be considered if dietary intake is insufficient.

6.2.1 BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw (ONJ) is a complication occurring in patients treated with bisphosphonates, especially the aminobisphosphonates. The prevalence of ONJ in cancer patients receiving intravenous bisphosphonates is 6-10%.[118]

Although bisphosphonates are effective in reducing pain and bone related events and have been used as standard treatment in the management of myeloma and breast cancer, there have been cautions on their long term use.[119] 4

In a non-systematic review of 368 cases of bisphosphonate-associated ONJ (85% of patients had multiple myeloma or breast cancer),[120] the most significant predisposing factors were found to be: 4

- use of aminobisphosphonates with increasing risk over time of exposure and higher doses
- history of trauma, dental surgery, or dental infection. Sixty per cent had some form of dento-alveolar surgery resulting in non-healing of the surgical site and necrosis of the bone.

Preventive strategies include treating all dental infection prior to commencement of treatment and avoiding invasive dental treatment when receiving IV bisphosphonates. The extent of risk for osteonecrosis in patients taking oral bisphosphonates has not been determined. There are no data available to suggest that discontinuation of bisphosphonates for patients requiring invasive dental treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating clinician should guide the management plan based on the individual risks/ benefits for the patient.

6.3 ANTIDEPRESSANTS AND ANTICONVULSANTS

6.3.1 ANTIDEPRESSANTS

Only two studies were identified which were carried out directly on patients with cancer pain. Evidence from studies in other patients has been reviewed as the same pathological mechanism of neuropathic pain is believed to be involved.

There is robust evidence from a systematic review of 31 randomised trials that tricyclic antidepressants are effective in the management of neuropathic pain (relative risk, RR 2.1; 95% CI 1.8 to 2.5).[121] Ten studies using amitriptyline indicate that although the optimal dose is not clear, regimens including up to 150 mg/day can be used effectively (NNT = 3.1; 95% CI 2.5 to 4.2); NNH for major harm for amitriptyline is 28 (95% CI 17 to 68). Two studies (100 patients) using desipramine show a NNT of 2.6 (95% CI 1.9 to 4.5) and three studies of imipramine (114 patients) show a NNT of 2.2 (95% CI 1.7 to 3.22). Tricyclic antidepressants are not effective in the treatment of human immunodeficiency virus (HIV) related neuropathies. 1++

Thirteen per cent of patients in the systematic review had to withdraw due to intolerable adverse effects.

Some studies have shown other tricyclic antidepressants may also be effective but the numbers in these studies were too small to make any definite conclusions.[121]

There is not enough evidence to support a recommendation on the use of selective serotonin reuptake inhibitors in neuropathic pain relief.

Three trials show that venlafaxine is effective in reducing neuropathic pain in doses of 75 mg, 150 mg and 225 mg (RR 2.2, 95% CI 1.5 to 3.1; NNT = 3.1, 95% CI 2.2 to 5.1).[121] No significant pain relief was reported in a placebo controlled trial of venlafaxine (30 patients) in doses below 75 mg.[122] One trial compared venlafaxine 225 mg (NNT 5.2) to imipramine 150 mg (NNT 2.7) in 40 patients. There were no significant differences in analgesic effect of the active drugs.[123] Side effect ratings were not different between the three treatments, although there was a trend toward more side effects during the two active treatments. 1+

Duloxetine is a potent dual action antidepressant which inhibits neuronal serotonin, norepinephrine and dopamine reuptake. It is licensed for treatment of peripheral diabetic neuropathic pain. Two RCTs demonstrate that a daily dose of 60 mg duloxetine reduces neuropathic pain with tolerable side effects.[124,125] Duloxetine is not considered as a first-line of therapy for neuropathic pain but may be considered by specialists when other treatments have failed or are unsuitable. 1++

6.3.2 ANTICONVULSANTS

Two systematic reviews were identified: one dealing with gabapentin in the management of pain (14 trials involving 1,468 patients)[126] and one dealing with various different anticonvulsants (23 trials involving 1,074 patients).[127] Only one study was carried out on patients with cancer pain though the results are considered generalisable with the same pathological mechanism of neuropathic pain involved. Pregabalin was not included in the systematic reviews. Both gabapentin and carbamazepine provided good pain relief in 66% of patients. There was no direct comparison between the two. The NNT for relief of neuropathic pain in patients with diabetic neuropathy varied according to the specific anticonvulsant used as follows: carbamazepine 2.3 (95% CI 1.6 to 3.8), gabapentin 3.8 (95% CI 2.4 to 8.7), and phenytoin 2.1 (95% CI 1.5 to 3.6). 1++

The NNH was calculated by combining studies regardless of condition treated. The NNH for major harm was not statistically significant for any drug compared to placebo and for minor harm was as follows: carbamazepine 3.7 (95% CI 2.4 to 7.8), gabapentin 2.5 (95% CI 2.0 to 3.2), and phenytoin 3.2 (95% CI 2.1 to 6.3). 1++

One RCT involving 137 patients indicated that pregabalin is better than placebo in relieving non-malignant neuropathic pain. Mean endpoint pain score was lower in the pregabalin group (4.62) than the placebo group (6.27; $p < 0.001$). The $\geq 50\%$ pain responder rate was higher with pregabalin than placebo ($p < 0.05$; NNT = 7.1).[128] 1++

One small RCT showed that pain relief was greater when gabapentin and morphine were combined. Mean daily pain (on a scale from 0 to 10, with higher numbers indicating more severe pain at a maximal tolerated dose of the study drug) was: 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin-morphine combination ($p < 0.05$ for the combination versus placebo, gabapentin, and morphine). Smaller doses of each drug were required than if administered singly, although the incidence of dry mouth was significantly higher ($p < 0.05$).[129] 1+

There is no direct evidence of comparative efficacy between anticonvulsants or between anticonvulsants and antidepressants.

The NNT for the antidepressant amitriptyline is similar to that of the anticonvulsants reviewed. The side effects are lower with an NNH of only 28. The choice of antidepressant or anticonvulsant should be based on concomitant disease, drug therapy and drug side effects experienced.

A **Patients with neuropathic pain should be given either a tricyclic antidepressant** *(eg amitriptyline or imipramine)* **or anticonvulsant** *(eg gabapentin, carbamazepine or phenytoin)* **with careful monitoring of side effects.**

6.4 KETAMINE

Ketamine is used in selected patients who have persistent pain that remains uncontrolled by other means and is prescribed by specialists in cancer pain. It may be indicated in neuropathic pain, ischaemic limb pain and refractory pain in cancer.[13,130] Generally ketamine is administered in addition to a strong opioid and if successful will restore opioid sensitivity. 2++ 4

When ketamine is commenced current practice is to reduce the opioid dose by 30-50%.

A systematic review[130] identified two small RCTs[131,132] (of 20 and 10 patients respectively) and 32 case reports which provided insufficient evidence about the benefits or harms of ketamine as adjuvant therapy. Small numbers and heterogeneity of trials precluded pooling of data. Ketamine appears to be less effective in neuropathic pain of longstanding duration (greater than three years). 2++

There is insufficient evidence on which to base a recommendation and further research is required to establish the role of ketamine as an adjuvant analgesic.

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

6.5 TOPICAL ANALGESIA

6.5.1 TOPICAL OPIOIDS

A small evidence base has suggested that topical opioids may be an effective local analgesic when applied to inflamed tissues. Four small RCTs involving the use of topical morphine (three trials, n = 33) or diamorphine (one trial, n = 13) were identified.

One RCT showed a dose response relationship for topical morphine. Pain relief from 0.2% morphine hydrochloride mouthwash on oral mucositis was greater than 0.1% strength mouthwash ($p = 0.023$). Both opioid strengths were more effective in relieving pain than placebo ($p = 0.006$). Time to good ($\geq 50\%$) pain relief following 0.2% morphine hydrochloride mouthwash was 28 ±12 minutes and duration of pain relief was 216 ±25 minutes.[133] 1+

Another small RCT (n = 5) compared single dose application of morphine sulphate 0.1% in Intrasite gel to placebo for the relief of pain from sacral sores (non-necrotic and not infected). Pain scores measured on VAS (0-100mm) was 47 ±11 for placebo and 15 ±11 for morphine ($p < 0.01$).[134] 1-

In a further study on hospice patients with non-necrotic, non-infected skin ulcers, morphine or its metabolites were undetectable systemically after applying morphine 10 mg in Intrasite gel daily in five out of six patients. In one patient (ulcer 60 cm^2) bioavailability was approximately 20% compared to subcutaneously administered morphine. Different carrier gels may influence the degree of opioid absorption.[135] 1-

Thirteen hospice inpatients with stage II or III pressure ulcers were randomised to receive either 0.1% diamorphine in Intrasite gel or placebo for local pain relief. Only seven patients (54%) completed the study. Six of these had improved pain scores at one hour ($p = 0.003$, four were pain free) and at 12 hours ($p = 0.005$, three were pain free) with diamorphine 0.1% gel. No patients were pain free during the placebo phase.[136] 1-

Topical opioids appear to have a locally rather than systemically mediated effect when applied to inflamed tissues. Numbers were small and caution should be exercised in drawing conclusions. There was insufficient evidence to support a recommendation.

6.5.2 LIDOCAINE 5% PLASTER

No evidence was identified for the use of lidocaine in patients with cancer pain. The lidocaine 5% plaster is indicated as a peripheral targeted analgesia for the treatment of postherpetic neuralgia.[137] 4

One double blind, crossover RCT recruited 58 patients with peripheral neuropathic pain syndromes and found a reduction of pain compared to placebo (NNT to achieve a 50% reduction in pain = 4.4; 95% CI 2.5 to 17.5).[138] The response rate was 31% with the plaster compared to 8.6% with placebo. The drop-out rate in this study was 33-35%. Those in the drop-out group were not included in the data analysis which is likely to bias the results in favour of the intervention. 1-

Another RCT showed lidocaine 5% plaster to be superior to placebo in the treatment of moderate/severe neuropathic pain.[139] 1+

No evidence was identified comparing the plaster directly with another active treatment or its role in polypharmacy.

6.5.3 CAPSAICIN

Capsaicin is the active component of chilli peppers that results in a local burning sensation on contact with skin followed by a period of reduced sensitivity and eventual persistent desensitisation in that local area. Topical formulations of capsaicin are used to treat pain from postherpetic neuralgia and diabetic neuropathy.

A systematic review was carried out to establish the efficacy and safety of topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorders.[140] Capsaicin was significantly better than placebo for the treatment of both neuropathic and musculoskeletal pain. In neuropathic conditions, the mean treatment response rate (percentage of patients with at least 50% pain relief) at four weeks for capsaicin 0.075% was 57% (range 53% to 75% in individual trials), and the mean placebo response rate was 42% (range 31% to 55%). The NNT was 6.4 (95% CI 3.8 to 21). These effects were maintained after eight weeks and were supplementary to unchanged oral therapy. In musculoskeletal conditions, the mean treatment response rate at four weeks for capsaicin 0.025% or plaster was 38% (range 34% to 42%), and the mean placebo response rate was 25% (range 17% to 37%). The NNT was 8.1 (95% CI 4.6 to 34). 1++

This review highlights the increased risk of local adverse events (eg burning, stinging and erythema) and adverse-event-related withdrawals with capsaicin compared to placebo. These were the same for neuropathic pain and musculoskeletal pain: 54% of patients using capsaicin displayed these adverse effects compared with 15% using placebo; the NNH = 9.8 (7.3 to 15.0). This translates as approximately one in three of those treated with capsaicin will experience adverse effects and would not have done so if administered placebo.

6.6 CANNABINOIDS

The use of cannabis or cannabinoids as analgesics in chronic painful conditions, including cancer is being researched. Nabilone is the only cannabinoid legally available in the United Kingdom and is licensed only for use in nausea and vomiting induced by chemotherapy.

The most potent cannabinoid is delta-9-tetrahydrocannabinol (THC) which is available in the United States but is not licensed for use in the United Kingdom. A systematic review identified five RCTs of 128 patients with nociceptive cancer pain.[141] The cannabinoids oral THC (5-20 mg) and intramuscular levonantradol (1.5-3 mg) were as effective as codeine (60-120 mg) in reducing nociceptive cancer pain. Benzopyranoperidine 2-4 mg was less effective than codeine (60-120 mg) and no better than placebo. 1++

Adverse effects with cannabinoids are common, dose related, and sometimes severe. Adverse effects associated with THC include mental clouding, ataxia, dizziness, numbness, disorientation, disconnected thought, slurred speech, muscle twitching, impaired memory, dry mouth, and blurred vision.[141] A dose of 20 mg THC is highly sedating in 100% of patients. At a dose of 10 mg THC was better tolerated but still resulted in more side effects than codeine at either 60 mg or 120 mg.[142] 1++ 1+

Two RCTs suggest that cannabinoids may be useful in the treatment of neuropathic pain in certain conditions.[143,144] One indicated that smoked cannabis reduced chronic neuropathic pain from human immunodeficiency virus associated sensory neuropathy.[143] The other found that an oromucosal spray containing THC and cannabidiol reduced central pain in multiple sclerosis.[144] 1+

No studies were found which assessed the effectiveness of cannabinoids on neuropathic pain due to cancer.

A **Cannabinoids are not recommended for the treatment of cancer pain.**

7 Treatment with opioid drugs

7.1 CHOICE OF OPIOID

7.1.1 MILD TO MODERATE PAIN (STEP 2 OF THE WHO LADDER)

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Weak opioids appropriate for use at step 2 of the WHO analgesic ladder are codeine and dihydrocodeine. There is logic in adding an opioid to paracetamol (eg cocodamol 30/500) or an NSAID or in adding an opioid to paracetamol plus an NSAID. This may reduce the dose of opioid required and hence reduce side effects.[145] — 3

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.[70,146,147] — 4

Codeine demonstrates a ceiling dose-response curve to pain relief.[148,149] Maximum analgesic effect is achieved at a dose of 240 mg/day. Increasing the daily dose beyond this does not increase analgesic effect but results in greater side effects. There is evidence that combinations of codeine 60 mg and paracetamol 600-1,000 mg are more effective than paracetamol alone at doses of 500-1,500 mg. No evidence was found in clinical trials or meta-analyses to support the superiority of cocodamol 8/500 over paracetamol alone. — 1+

Approximately 7% of Caucasian people, 3% of black people and 1% of Asian people have poor or absent metabolism of codeine resulting in a reduced or absent analgesic effect.[150] — 4

There is limited evidence from small studies to indicate that tramadol should be considered as a step 2 analgesic.

An RCT of 40 patients using patient-rated pain scores compared equianalgesic doses of morphine and tramadol (morphine 1:tramadol 4).[151] No significant differences were observed between analgesic efficacy of tramadol and morphine treatment with immediate release (week one) or modified release preparations (at weeks three and five). In patients with bone pain, pain intensity was significantly greater before treatment in the tramadol group, although no differences were found between the drugs during treatment. Tramadol was less effective in relieving neuropathic pain at week one ($p < 0.05$) although this difference was not maintained. During follow up, five patients in the tramadol group required medication change to morphine due to an increase in pain intensity. Tramadol was recommended for use in moderate pain intensity (VAS 3-6), morphine for severe pain VAS 7-10. 80% of patients receiving either morphine or tramadol preferred the modified release preparations of these drugs over the immediate release preparation. — 1+

Evidence from an open uncontrolled trial of 146 patients suggests that slow-release tramadol may be effective as a step 2 analgesic for controlling chronic cancer pain.[152] There is insufficient evidence available to make a recommendation on the use of tramadol. — 2+

D

For mild to moderate pain, *(score 3-6 out of 10 on a visual analogue scale or a numerical rating scale)* **weak opioids such as codeine should be given in combination with a non-opioid analgesic.**

7.1.2 MODERATE TO SEVERE PAIN (STEP 3 OF THE WHO LADDER)

Strong opioids in use in palliative care in the UK are morphine, alfentanil, buprenorphine, diamorphine, fentanyl, hydromorphone, methadone and oxycodone. Methadone has a long and unpredictable half life, with considerable inter-individual variation, and should be initiated only within specialist settings with careful monitoring. Detailed information on using methadone for cancer pain is not included in this guideline. Practitioners are advised to seek advice from specialist palliative care professionals for all opioids with which they are not familiar.

The number of strong opioids and range of formulations marketed has increased within the last few years, with further developments anticipated. Some opioids previously used for other indications, eg anaesthesia or intensive care, are now in use in palliative care settings.

Although some of the newer or less commonly used opioids tend to be initiated in specialist units or following specialist advice, there is an increasing trend for patients to be cared for in the community. Individual practitioners in generalist settings may use strong opioids relatively infrequently, and consequently may find the range of strong opioids and newer formulations confusing.[153,154] A Department of Health report highlights the importance of clear guidance for the prescribing and use of strong opioids as a component of reducing the risks of potentially serious medication errors.[155]

3
4

Morphine

The first line opioid for oral use in severe cancer pain is morphine.[156] The majority of patients tolerate oral morphine well and, due to the likelihood that patients will use medication chronically, the oral route is preferable to parenteral or rectal administration. The systemic bioavailability of morphine by the oral route is poor, with wide variation between individuals, but with individual dose titration a satisfactory level of analgesia can usually be achieved. The efficacy and safety of morphine is well established in clinical practice[3, 90] and the wide variety of morphine formulations available in the United Kingdom allows flexibility in dosing intervals.

3
4

There is a lack of evidence from high quality comparative trials that other opioids have advantages in terms of either efficacy or side effects which would make them preferable to morphine for first line use in cancer pain. Small trials lack the statistical power to demonstrate superiority of one opioid over another, and extrapolation of side effect profiles from trials in non-cancer populations to those with advanced cancer may not be relevant.[157] Familiarity with the use of morphine by most practitioners is an additional consideration for patient safety.

D **Oral morphine is recommended as first line therapy to treat severe pain in patients with cancer.**

Diamorphine

Diamorphine is ten times more soluble in water than morphine, and is easier to administer at higher doses.[158,159] For subcutaneous administration, diamorphine is the preferred opioid for the control of severe pain.

4

D **Diamorphine is recommended as first line subcutaneous therapy to treat severe pain in patients with cancer.**

Hydromorphone

Hydromorphone is available as both immediate release and modified release capsules (12 hourly), allowing titration in a similar way to morphine, but the lack of a high strength immediate release capsule can pose difficulties for patients prescribed high doses. The pharmacokinetic properties are similar to morphine, and there is wide interpatient variation in bioavailability. There is no licensed oral liquid in the UK but for patients with swallowing difficulties, the capsules can be opened and the contents sprinkled on a spoonful of cold soft food.

Oxycodone

Oxycodone is available as immediate release capsules, modified release tablets and oral liquids. It has more predictable bioavailability than morphine (60-87% for oxycodone vs 15-65% for morphine). The modified release tablets have a biphasic pharmacokinetic release profile showing two peaks after oral administration. This allows onset of analgesia within an hour of ingestion and an analgesic duration of 12 hours.

Transdermal fentanyl

For those with stabilised severe pain who express a preference for a patch formulation or those with swallowing difficulties or intractable nausea and vomiting, fentanyl transdermal patches may be appropriate provided the pain is stable.

A prospective multicentre study evaluating efficacy, patient satisfaction, and safety aspects during conversion from the original transdermal fentanyl gel reservoir patches to a newer matrix formulation was carried out on 46 outpatients with chronic pain from both malignant and non-malignant origin.[160] This study concluded that there was no difference in pain intensity, sleep interference, adverse events between the time of using the last gel patch (72 hours) and the time of using the first two matrix patches (144 hours). The median dose of fentanyl from baseline to study endpoint was 50 mcg/hour (range 25-500 mcg/hour). Due to better adhesion and fewer skin sensitivity reactions patients preferred the matrix patch. Outpatients may be safely switched directly to the matrix from the gel patch. 1++

One randomised, two way crossover study demonstrated similar pharmacokinetics and tolerability between the gel and matrix systems.[161] 2++

☑ As patches vary considerably in their appearance, and to avoid the risk of patient confusion, patients should not be changed from one formulation or make to another without adequate counselling.

See section 7.5 for conversion ratios between different opioids and routes of administration.

7.1.3 FORMULATION OF MORPHINE

The range of morphine: modified and immediate release tablets and capsules, and immediate release liquids available in the UK is extensive, making it possible to find a suitable oral formulation for most patients.

Immediate release formulations

Immediate release morphine formulations 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 7.1.4*). Immediate 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.[162] 4

Modified release formulations

Modified release morphine formulations have a slower onset and later peak effect. Many of the twice daily preparations have an onset of action of one to two 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 and are most appropriately used for maintenance or control of stable background pain. Modified release preparations generally do not allow rapid titration for patients in severe pain, due to slow onset and the long dosing intervals.[163] 4

7.1.4 BREAKTHROUGH PAIN

Breakthrough pain is defined as a transient flare of pain of moderate or severe intensity arising on a background of controlled pain.[9]

Breakthrough pain is characteristically:[164]

- rapid onset (peaks within one to three minutes)
- of moderate to severe intensity
- of short duration (median 30 minutes, range 1-240 minutes)
- associated with worse psychological outcomes
- associated with poor functional outcome
- associated with a worse response to regular opioids
- associated with negative social and economic consequences.

Breakthrough pain can be spontaneous or incident. Spontaneous pain is sudden and unexpected. Incident pain is associated with an action such as breathing, movement or micturition and can be anticipated. This distinction is important for therapeutic management. For example, breakthrough pain medication may be taken in anticipation of an episode that is likely to precipitate incident pain, such as walking or having a wound dressing changed.

Differentiation between breakthrough pain and 'end of dose failure' of regular around the clock (ATC) analgesia is important. End of dose failure occurs at a similar time each day usually shortly before the next dose of regular analgesia and is caused by an inadequate dose of ATC analgesia. An increase in the ATC dose will address end of dose failure.

Convention has established an effective means of titrating the ATC opioid by using the number of breakthrough doses used in the preceding 24 hours and adding all or a proportion of this to the latest ATC dose. Empirically, the widely accepted ratio of the breakthrough dose to the ATC medication has been 1:6, ie equivalent to the four hourly opioid dose.[156] In patients where the intent is to gain control of pain, traditionally there is a dual titration of the ATC and the breakthrough medication with a constant ratio maintained between the two as the doses increase. 4

The pharmacokinetics of immediate release oral opioids are such that onset of analgesia is reached after 20-30 minutes following oral ingestion. The plasma elimination half life of morphine is 2.2 hours.[165] The opioid for treating breakthrough pain should ideally have pharmacokinetics which mirror the time features of the majority of patients' specific breakthrough pain, ie rapid onset of action, high analgesic potency, fast offset of action and oral formulation.

The only randomised trials of analgesics for treating breakthrough pain have involved the use of oral transmucosal fentanyl citrate (OTFC) with an upward titration method independent of the ATC dose to establish an effective analgesic dose.[164,166-168,169] These studies have demonstrated that OTFC can be safe and effective in the treatment of episodes of breakthrough pain with rapid onset and offset in patients with cancer who are receiving strong opioids. Analysis of these studies shows that of the 391 recruited, only 281 (72%) were stabilised on an effective OTFC dose and entered the randomised double blind phase. A further 45 withdrew leaving 236 (60%) of those recruited to complete the study. This buccally administered formulation has a rapid on- and offset of action. Up to 50% of the total reduction in pain intensity occurs within the first 15 minutes after administration. Duration of action is about two hours.[164] No relationship was found in any of these studies between the effective therapeutic dose of OTFC and the ATC dose of strong opioid. 1^{++} 1^{+} 1^{-}

These studies indicate that to achieve control of rapid onset and offset breakthrough pain using fast acting opioid analgesics to a level determined acceptable by the patient, the dose of breakthrough medication is not a fixed proportion of the ATC opioid but should be titrated until a successful dose is found.

One RCT compared the effectiveness of OTFC and immediate release morphine sulphate (MSIR) for treating breakthrough pain.[168] The main outcome measure was difference in pain score immediately before taking medication and at 15 minute intervals following medication up to 60 minutes (pain intensity differences - PID). Both opioids were effective in reducing breakthrough pain but a greater proportion of episodes treated with OTFC had a > 33% change in 15 minute PID than MSIR (OTFC 42.3% vs. MSIR 31.8%). This indicates a more rapid onset of action for OTFC in comparison to MSIR. However, the successful MSIR dose was not arrived at in the same protocol-driven manner as the successful OTFC dose; a number of days had elapsed between the time the MSIR dose was set and the OTFC dose titrated, over which time the breakthrough pain might have worsened; no relationship was found between the OTFC and MSIR doses; the type of breakthrough pain treated was not identified in the study and only 56% of the individuals recruited into the study had data available for analysis by the study completion. During the OTFC titration phase patients who could not arrive at a satisfactory OTFC dose were excluded. 1-

Both MSIR and OTFC can be effective at reducing breakthrough pain but there is insufficient evidence to recommend one opioid over the other. Further studies are required comparing carefully titrated doses of MSIR and other immediate release opioids in incident and spontaneous breakthrough pain.

Alfentanil is used by some specialists as a treatment for breakthrough pain via the intranasal or sublingual routes. These routes of administration are unlicensed and there is insufficient evidence to support their use.

D **Patients with moderate or severe breakthrough pain should receive breakthrough analgesia.**

D **When using oral morphine for breakthrough pain the dose should be one sixth of the around the clock morphine dose and should be increased appropriately whenever the around the clock dose is increased.**

☑ When using oral transmucosal fentanyl citrate for breakthrough pain the effective dose should be found by upward titration independent of the around the clock opioid dose.

7.1.5 BIOEQUIVALENCE OF MODIFIED RELEASE FORMULATIONS

There is increasing pressure within the UK, on grounds of cost-effectiveness, to prescribe medicines generically. Arising from this, concerns have been raised in clinical practice that some patients experience differences in analgesia and/or side effects when changed from one brand to another, and may also have an increased risk of medication error due to confusion between the appearance of different products.

Within the European Union, the European Agency for the Evaluation of Medicinal Products (EMEA) details a requirement for the inclusion in licensing applications of bioequivalence studies for modified release dosage forms in accordance with a specified guideline.[170] Such studies are intended to show pharmaceutical and bioavailability similarities, "to such degree that their effects, with respect to both efficacy and safety, will be essentially the same". Licensed modified release oral morphine preparations marketed in the UK are thus deemed bioequivalent at the time of licensing. 4

A Cochrane review of oral morphine for cancer pain looked at comparative studies between different oral morphine preparations.[171] None of the four reported studies comparing two brands of modified release oral morphine compared brands which are both marketed in the UK. Most of the studies comparing different oral morphine preparations (and some of these were comparison of modified release with quick release preparations) were designed to show equivalence of products, and it was unclear whether they were sufficiently powered to detect clinically meaningful differences between formulations. It is not possible to draw any firm conclusions about the equivalence or otherwise in clinical practice of different modified release morphine preparations. 1++

A Department of Health report highlights reports of serious errors arising from confusion between different oral formulations of the same opioid.[155] One of the recommendations in the report was to include the brand name of oral modified release preparations on the prescription and dispensing label to aid in the identification of the correct formulation. 4

☑ To minimise the potential risks to patients of errors occurring between different brands and formulations of oral morphine preparations, prescribers should gain familiarity with one brand of modified release oral morphine for routine use. It may be appropriate to consider others when individual patient-specific factors warrant a different product.

☑ Prescribers and pharmacists should ensure that patients understand any intended changes in the appearance of their medicine to ensure both adequate analgesia and safety.

7.1.6 PATIENTS WITH RENAL IMPAIRMENT

Deteriorating kidney function is commonly seen in palliative care patients due to old age, concomitant drug therapy or disease. Dehydration may result rapidly if patients are very drowsy and not encouraged to drink adequate fluids. Dehydration and renal impairment increase the potential for opioid toxicity. Early signs of opioid toxicity include subtle agitation, reports of vivid dreams, pseudo-hallucinations usually at the periphery of the visual field and myoclonus.

There are some differences between the opioids in terms of their metabolism and excretion, some metabolites may be pharmacologically active and, if excreted renally, may contribute to toxicity. There is a lack of clinical evidence to determine the relative safety of different opioids in patients with renal impairment, including those receiving dialysis.

The only systematic review identified compared the consistency of information on classification of degree of renal impairment and dose adjustment for drugs in renal impairment in four standard reference sources.[172] Three of these texts are commonly used in the UK and considered reliable sources of information on medicines: The British National Formulary (BNF),[173] Martindale: the Complete Drug Reference,[158] and Drug Prescribing in Renal Failure.[174] The review found considerable variation in definitions of renal impairment and recommendations for dose adjustment between the sources. Comparisons of the consistency of information in these sources for opioid prescribing in renal impairment is not reported in the review, but the need to use caution in interpreting secondary sources of information is evident. Dose adjustment recommendations can only provide an initial guide, and regular reassessment and dose adjustment according to the patient's clinical condition is imperative. 4

No systematic review of the use of opioids in patients with renal impairment was identified. Reviews of opioids in renal impairment tend to be based on pharmacokinetic profiles of the drugs rather than reporting clinical outcomes other than adverse effects.

Reports of toxicity for a range of opioids in patients with renal impairment are discussed in conjunction with changes in opioid pharmacokinetic profiles in non-systematic reviews.[175-177] Pharmacokinetic studies have demonstrated accumulation of renally excreted opioid metabolites. Generally toxicity is related to the activity of these metabolites or the parent drug. 4

☑ In patients with poor or deteriorating kidney function, the following are of considerable importance to prevent or manage toxicity:

- choice of opioid
- consideration of dose reduction and/or an increase in the dosage interval
- change from modified release to an immediate release oral formulation
- frequent clinical monitoring and review.

Codeine and dihydrocodeine

Renal clearance of codeine and its metabolite codeine-6-glucuronide is reduced in patients with renal impairment.[176] In addition, codeine is metabolised to morphine and its metabolites which also accumulate in patients with renal impairment. | 4

The pharmacokinetic profile of dihydrocodeine is similarly altered in patients with renal impairment.[177] | 4

Toxicity from codeine and dihydrocodeine has been reported in patients with renal impairment, and caution in their use is required.[176-178] | 4

Morphine

Morphine is metabolised mainly in the liver and the metabolites largely excreted renally. Morphine-6-glucuronide is pharmacologically active as an analgesic. Toxicity in patients with poor renal function is well reported.[175-178] This is due to accumulation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The ratio of the main metabolites of morphine, M3G and M6G to morphine itself, have been shown to increase by 5.5 and by 13.5 respectively in the presence of renal impairment.[179] Gradations of dose reduction and decreased frequency of administration are required depending on the degree of renal impairment.[176] Toxicity due to accumulation of metabolites in cerebrospinal fluid can take several days to resolve after morphine is discontinued.[178] | 2+ 4

Oxycodone

Oxycodone's principal metabolites are oxymorphone and noroxycodone which are excreted renally. The contribution of the metabolites to the pharmacological activity of oxycodone is uncertain but thought to be small. Reduced elimination of oxycodone in renal impairment has been reported[175, 176] and while excretion of metabolites is severely impaired, there is little data on the clinical effects of accumulation in renal failure.[178] Until this data is available oxycodone should be used with care in patients with renal impairment. | 4

Hydromorphone

Hydromorphone is metabolised in the liver, principally to hydromorphone-3-glucuronide. All metabolites are excreted renally with a small amount of free hydromorphone. Evidence for the safety of hydromorphone in renal impairment is inconsistent.[178] | 4

One limited study compared the efficacy and outcomes of switching from another opioid to hydromorphone in 26 patients with normal renal function and 29 with renal impairment.[180] The study included inpatients in a palliative care unit most of whom had cancer. There was a significant difference ($p < 0.0001$) in renal function between the two groups, but no significant difference between the groups in reasons for switching to hydromorphone or dose of opioids. After the switch, over 80% of patients showed an improvement in side effect profile. The study report did not specify how the severity of side effects was assessed nor the method of pain assessment. At least 30% of those with renal impairment were prescribed hydromorphone for a month or more. Although the authors found hydromorphone to be safe and effective in patients with renal impairment, they did note that their conclusions were preliminary, and acknowledged the limitations of the criteria used for renal impairment (urea > 10.5 mmol/l and/or creatinine ≥ 101 mmol/l). | 3

Case reports have revealed examples of hydromorphone toxicity in patients with renal failure [176, 178] and evidence from a single case report of accumulation of hydromorphone-3-glucuronide in chronic renal failure.[181] | 3

Further research is needed to establish the safety profile of hydromorphone in renal impairment.

Fentanyl

Fentanyl is metabolised in the liver to compounds thought to be inactive and non-toxic, with less than 10% excreted unchanged in urine. Whilst some reviews have reported studies concluding that no dose adjustment is needed in patients with renal impairment[176,177] an increased elimination half life has been reported in critically ill patients with renal failure.[176] Monitoring patients with renal failure for signs of gradual accumulation of the parent drug would seem prudent.[178] 4

Alfentanil

Alfentanil, a synthetic derivative of fentanyl, is less potent than fentanyl but about 10 times as potent as diamorphine with a rapid analgesic effect and short duration of action. It is metabolised in the liver, with urinary excretion of the metabolites (which are thought to be inactive) and less than 1% of a dose excreted unchanged, and considered safe for use in renal impairment.[176] It is available as an injection which can be administered as a continuous subcutaneous infusion although it is not licensed for subcutaneous use. 4

Buprenorphine

Buprenorphine is available in a patch formulation. It is metabolised mainly to norbuprenorphine, the only metabolite thought to have analgesic activity, and which is 40 times less potent than the parent compound.[177] Unchanged drug is mainly excreted in the faeces, and metabolites in the urine. Buprenorphine is considered generally safe to use in renal impairment as the pharmacokinetics are largely unchanged.[176,177] 4

Tramadol

Tramadol is extensively metabolised in the liver to one active metabolite, O-demethyl tramadol.[176,177] Unchanged tramadol and the active metabolite are both eliminated mainly by the kidneys and will accumulate in renal impairment, requiring dose reduction and an increase in the dosing interval according to the degree of impairment. 4

In patients undergoing renal dialysis, opioid use is further complicated by the removal of some opioids and their active metabolites by dialysis. For these opioids, supplemental doses of short acting analgesics may therefore be required during or after dialysis sessions to maintain pain control.

C **In the presence of reduced kidney function all opioids should be used with caution and at reduced doses and/or frequency.**

☑ Alfentanil, buprenorphine and fentanyl are the safest opioids of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 ml/min/1.73 m^2).

☑ Specialist palliative care advice should be sought for the appropriate choice, dosage and route of opioid in patients with reduced kidney function.

7.2 ADMINISTRATION OF OPIOIDS

7.2.1 ROUTE OF ADMINISTRATION OF OPIOIDS

In the majority of patients taking opioids, oral delivery is preferred as it is effective and simple. Transdermal, subcutaneous or very occasionally intravenous routes are necessary when patients are unable to take the opioid orally, for example due to vomiting or where the patient is unable to swallow. Epidural and intrathecal routes are considered when pain is responsive to opioids but the dose required is producing undue toxicity despite switching opioids and using optimal adjuvants.

A one way crossover study of 40 patients examining intravenous and subcutaneous routes of administration of morphine showed them to be equianalgesic with similar side effect profiles when given as a continuous infusion.[182] 3

Transdermal opioid patches can be a useful alternative to intravenous or subcutaneous infusions for patients unable to swallow oral medication. Due to the long duration of action of each patch they are only recommended for patients whose pain is stable.

☑ The oral route should be used for administration of opioids, if practical and feasible.

D **Continuous subcutaneous infusion of opioids is simpler to administer and equally as effective as continuous intravenous infusion and should be considered for patients unable to take opioids orally.**

☑ In patients with stable pain who are unable to swallow oral medication transdermal administration of opioids should be considered.

SIGN 44

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. Avoid administering irritant drugs subcutaneously, eg diazepam, chlorpromazine, prochlorperazine. Information from published or peer reviewed studies of chemical and/or physical stability is provided at Annex 1.

A prospective survey involving 15 UK palliative care services examined the current practice of combining drugs in syringe drivers.[183] Of 336 syringes, the majority contained two or three drugs and only one fifth contained only one drug. Laboratory physical and chemical compatibility data was available for less than half of the most frequently used combinations. 3

Factors which may influence whether mixtures of drugs are compatible include concentration of each drug, salt form, additives (which may vary with different manufacturers or formulations), diluent, order of mixing drugs, temperature and pH.[184] 4

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

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

☑ Drug solutions for subcutaneous infusion should be diluted as much as possible in order to reduce the likelihood of drug incompatibility and minimise irritation the subcutaneous site.

7.2.2 SCHEDULE OF ADMINISTRATION OF OPIOIDS

Immediate release oral preparations of morphine, oxycodone and hydromorphone require administration every four hours to maintain a continuous analgesic effect. Modified release preparations of these drugs have been developed to allow once daily (in the case of morphine) or 12 hourly dosing.

There is no statistically significant difference between four hourly dosing of oral immediate release morphine, 12 hourly dosing of oral twice daily modified release morphine and 24 hourly dosing of oral once daily modified release morphine in efficacy of pain control.[185,186] Modified release medications have been shown to improve compliance and reduce sleep disturbance. The use of eight hourly dosing of the modified release morphine preparations intended for twice daily use is rarely indicated.[185] 1+ 4

Similarly, with respect to pain relief there is no statistically significant difference between four hourly dosing of oral immediate release oxycodone and 12 hourly dosing of oral twice daily modified release oxycodone.[187] 1+

D **Patients with stable pain on oral morphine should be prescribed a once or twice daily modified release preparation.**

D **Patients with stable pain on oral oxycodone should be prescribed a twice daily modified release preparation.**

☑ Patients with stable pain on oral hydromorphone should be prescribed a twice daily modified release preparation.

7.2.3 CONVERSION RATIOS BETWEEN DIFFERENT ROUTES OF ADMINISTRATION OF OPIOID DRUGS

Current practice for converting opioid doses between different routes of administration is based on pharmacokinetic data for individual opioids, such as bioavailability after oral administration, and on expert opinion and experience. The recommendations from the European Association for Palliative Care state that the relative potency ratio of oral to parenteral morphine is controversial, and note the variability between patients.[156] For some opioids, there are differences between the ratios specified by the manufacturer, and those based on expert opinion following use in clinical practice.[13] 4

An open, single dose, randomised crossover study in 24 healthy male volunteers compared the pharmacokinetics of oxycodone normal release oral liquid 5 mg/5 ml with oxycodone injection 10 mg/ml administered as a subcutaneous, intravenous, or intramuscular bolus dose.[188] The study found that oral oxycodone exhibits pharmacokinetic characteristics supporting the practice of reducing the oral oxycodone dose by 50% when converting to subcutaneous, intramuscular or intravenous oxycodone (*see section 7.5.1*).

7.3 TITRATING OPIOIDS

A careful individual assessment of pain control, degree of side effects and total amount of opioid required, including breakthrough doses, in the previous 24 hours must be made daily prior to prescribing. Starting doses of oral morphine in opioid-naive patients are generally of the order of 5 to 10 mg four hourly in young and middle aged people and 2.5 to 5 mg four hourly in the elderly.[156] Conventional practice is to commence an immediate release formulation of opioid which allows pain to be controlled more rapidly. This also allows earlier assessment and titration up or down if necessary. An example of opioid dose titration is shown in table 3. 4

Table 3: Example dose titration

Regular opioid dose	Frequency of dose	Breakthrough dose	Frequency of breakthrough episodes	Total opioid in 24 hours	New titrated dose
10 mg morphine sulphate (immediate release)	Four hourly	10 mg morphine (immediate release)	Three times daily	(10x6) + (10x3) = 90 mg	15 mg morphine sulphate, four hourly

Once pain has been controlled the four hourly dose may be converted to a 12 hourly modified release dose by dividing the effective total 24 hour dose by two. In the example in table 3 the new modified release morphine dose would be 45 mg twelve hourly with 15 mg of immediate release morphine for breakthrough pain.

Care should be taken when calculating a new regular dose for patients who are pain free at rest but have pain on movement (incident pain). If all the analgesia for this 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, pre-emptive analgesia for movement related pain, maximising non-opioid and adjuvant analgesics and consideration of other treatment modalities such as radiotherapy, anaesthetic nerve blocks, and stabilising surgery.[189,190] 4

7.4 SWITCHING BETWEEN STRONG OPIOIDS

Use of the WHO analgesic ladder has been shown to be effective in managing pain in about three quarters of patients with cancer (*see section 5.2.2*). Despite dose titration and appropriate management of predictable side effects, a minority of patients at step 3 of the WHO ladder have inadequate pain relief, persistent unacceptable side effects, or a combination of the two. Changing to a different opioid in an attempt to improve the balance between efficacy and side effects and thus achieve good pain control is termed opioid switching. All opioids have the same spectrum of side effects but the intensity of these side effects can vary between individuals exposed to different opioids.[191] 1^{++}

There is an increasing tendency in clinical practice to switch between opioids but the rationale for this in individual patients is not always clear, appropriate or well documented. It can lead to the use of newer opioids which may be unfamiliar to many practitioners, with associated risks of medication errors. There can also be significant cost implications.

Symptoms such as nausea or drowsiness which may occur in patients commenced on a strong opioid or who have had a recent dose increase often resolve within days and are not an indication for a switch of opioid. In most instances, side effects will resolve and may require a temporary reduction in opioid dose followed by slower dose titration and use of additional medication to control predictable side effects. Attention should also be given to adequate holistic assessment and management of pain rather than simply increasing doses of opioids. It can be difficult to differentiate between apparent adverse effects to opioids, and similar symptoms related to other aspects of the patient's disease; an accurate history is important.

A systematic review investigating the evidence base for opioid switching in patients with pain identified 52 studies of poor methodological quality, comprising 23 case reports, 15 retrospective studies/audits and 14 prospective uncontrolled studies.[192] Fifty of these were in patients with cancer. Inconsistencies in reporting of dose conversion ratios and the reasons for opioid switching were noted, as well as a lack of clarity that the initial opioid was being given at a high enough, but tolerable, dose to achieve maximum pain relief. Other confounding variables which were not well addressed in the majority of the studies included a change in route as well as drug, different types of pain, use of adjuvant analgesics, and a failure to consider other causes of toxicity. 2^{++}

Evidence to support the practice of opioid switching to improve pain relief and/or drug tolerability is anecdotal or based on observational and uncontrolled studies. Despite this, for patients with inadequate pain relief and persistent intolerable opioid-related toxicity/adverse effects, a switch to an alternative opioid may be considered in an attempt to achieve a better balance between pain relief and side effects.

A further systematic review which identified 31 prospective and retrospective studies confirmed the findings of the earlier review.[97] 2^{++}

One prospective study recruited 186 patients receiving oral morphine at two sites of a UK tertiary cancer centre.[193] 138 patients had a good response to morphine. 48 patients had inadequate pain control and/or unacceptable side effects. Pain was assessed objectively using Modified Brief Pain Inventory on an NRS of 0-10. Toxicity scores were recorded on four point scale: 'not at all', 'a little', 'quite a bit', 'very much'.

At baseline (before switching) those patients who went on to switch to an alternative opioid (switchers) had higher pain scores and obtained less pain relief than those who responded well to morphine (responders) but there was significant overlap in the ranges between the groups: average pain, switchers 5 (0-10), responders 2 (0-8), $p < 0.0001$; worst pain, switchers 8 (2-10), responders 5 (0-10), $p < 0.0001$; pain relief, switchers 60% (0-100%), responders 80% (20-100%), $p < 0.0001$. 3

Those who did not achieve a good clinical response on morphine experienced more side effects than the morphine responders (moderate/severe confusion, score 2 or 3, 25/48 versus 16/138, $p < 0.0001$; severe drowsiness, score 3, 27/48 versus 13/138, $p < 0.0001$; nightmares, score 2 or 3, 10/48 versus 4/134, $p < 0.0001$; severe nausea, score 3, 9/48 versus 8/138, $p < 0.05$). The commonest reasons for switching were pain, confusion and drowsiness, nightmares or nausea. The strongest association with switching was in patients who were both confused and had a drowsiness score > 2 ($p < 0.0001$).

A single switch to oxycodone was reported as successful in 37 of 47 patients (79%), although details of objective evidence of how this was assessed are not reported, nor is the time period within which assessment of benefit was made. Two patients required two switches and two patients required three switches before achieving a successful outcome. 41/47 switchers achieved a good clinical outcome.

Although uncommon, 24-36 hours after switching from one opioid to another, opioid withdrawal symptoms may occur. These can be managed by administering a small dose of the previous opioid.[194] 3

In the absence of strong evidence supporting the practice of opioid switching, the guideline development group suggests that before considering a switch to another strong opioid, a thorough holistic reassessment of pain and pain management should be undertaken for individual patients who have inadequate pain control despite appropriate dose titration and /or persistent intolerable side effects which do not resolve with appropriate intervention.

☑ Patients prescribed strong opioids who have inadequate pain control and/or persistent intolerable side effects should receive a thorough holistic reassessment of pain and pain management.

☑ Patients in whom pain is not controlled despite optimisation of dose and opioid-related side effects preclude further upward titration should be switched to a different opioid.

7.5 CONVERSION RATIOS

7.5.1 CONVERSION RATIOS BETWEEN DIFFERENT OPIOID DRUGS

There is a need to calculate equivalent doses of opioids in two situations. Firstly when patients step up from a weak opioid to morphine; and secondly if the need arises to switch between strong opioids (*see section 7.4*).

There is evidence of wide variation in equianalgesic dose ratios (EDRs) between strong opioids reported in published studies, manufacturers' literature and reference sources.[180,195,196] An appreciation of the reasons for this is important to ensure that switching between opioids is carried out safely without overdosing, whilst as far as possible providing an acceptable level of analgesia. 2+ 3 4

Dose conversion ratios between opioids are commonly derived from single dose studies, and because of the role of metabolites which take longer to reach a steady state, the applicability of these ratios to chronic opioid administration is questionable.[197] The difficulties in determining EDRs include the differences in bioavailability of oral opioids between individuals and between different opioids and inadequacies of the available literature (there are limited data, small sample sizes, heterogeneity of published studies and determination of equianalgesic dose is often not the primary outcome measure). Studies rarely take into account active metabolites which may contribute to analgesia and/or toxicity.

Hydromorphone

A systematic review of 43 studies on hydromorphone was unable to determine a specific equianalgesic ratio between morphine and hydromorphone.[198] A retrospective study in 55 adults used a conversion ratio of 7.5 to 1 from oral morphine to oral hydromorphone in accordance with the manufacturer's recommendation of between 5-10 to 1 but noted that many patients had their dose of hydromorphone increased shortly after the change. The study suggests that the conversion factor may be nearer to 5:1 as suggested elsewhere.[180] 2++ 2+

Oxycodone

An RCT compared the relative potencies of single doses of modified release oxycodone and modified release morphine in 169 patients with postoperative pain.[199] Results supported the manufacturer's recommendation when converting from oral morphine to oral oxycodone to give an initial oxycodone dose of one half of the oral morphine dose, followed by appropriate individual dose titration. The trial noted that different potency ratios have been reported in multiple dose settings. 1+

Methadone

Methadone is very occasionally used as an alternative opioid in specialist palliative care units and the difficulties of establishing equivalent doses when converting between opioids are even more pronounced with methadone. Findings from three small studies[195,200,201] involving fentanyl and methadone by various routes, and two others[202,203] where conversions of other opioids to or from methadone were undertaken, highlight the importance of dose titration up or down after switching. The conversion ratio may differ according to the direction of switch. All the conversions to methadone were carried out within specialist palliative care inpatient units with careful monitoring. Methadone initiation in other settings without specialist advice is not recommended. 1+ 3

Fentanyl

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Fentanyl is a powerful μ-receptor agonist. The main route of regular administration for fentanyl in the UK palliative care setting is via a transdermal patch. 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.

Each new patch is applied for 72 hours, providing continuous delivery of fentanyl. There is a lag time after application of the first patch to onset of analgesia, and to achieving steady state plasma levels following patch initiation or dose change. This makes dose titration of transdermal fentanyl difficult, and it is recommended that intervals of at least three days should be used for dose titration.[204] 3

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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).[205] 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 immediate release oral morphine or intermittent or continuous subcutaneous diamorphine as dictated by the clinical situation. 4

Manufacturers list a wide range of oral morphine doses corresponding to each strength of patch (*see Annex 2*), with a resultant wide range in conversion ratios of oral morphine to transdermal fentanyl (approximately 100:1 to 150:1). Studies confirm the wide range of ratios and note that ratios which are conservative in one direction may be excessive in the reverse direction.[197, 204] Frequent reassessment and dose titration are indicated after patch initiation or dose change, in conjunction with prescribing a short acting opioid to be taken for breakthrough pain.

☑ When converting from an oral strong opioid to transdermal fentanyl:

- if taking 4 hourly oral opioid, continue for 12 hours after applying transdermal patch
- if taking 12 hourly oral opioid, give last dose when first transdermal patch is applied
- if taking 24 hourly oral opioid, apply first transdermal patch 12 hours after last dose.

Variability between patients accounts for much of the variation observed in EDRs for different opioids. For example, the bioavailability of oral morphine varies fourfold from 15-64%;[13] nutritional and biochemical status affect protein binding; renal and hepatic impairment alter excretion and drug interactions may be a factor. The multidimensional nature of pain may also contribute to the wide ranges found.

4

Tables of dose conversion ratios should be used only as an initial approximate guide. Particular attention to monitoring and dose titration up or down is needed when: [13]

- switching between opioids at high doses
- there has been a recent rapid escalation of the first opioid
- switching to methadone (in consultation with palliative care specialists).

A set of conversion ratios for commonly used opioids is shown in table 4. It should be noted that these conversion ratios, based on available evidence, are conservative in the direction specified; if converting in the reverse direction, a reduction in dose of one third should be used following conversion, or specialist advice sought.

☑ When converting from one opioid to another, regular assessment and reassessment of efficacy and side effects is essential. Dose titration up or down according to pain control and/or adverse effects may be required.

Table 4: Suggested dose conversion ratios in the direction specified

These are initial suggested conversion ratios only; the patient's clinical condition should be taken into account and breakthrough analgesia prescribed as necessary.

Following opioid conversion, monitoring and dose adjustment up or down according to efficacy and side effects is required.

(Converting from) Current opioid	**(Converting to) New opioid and/ or new route of administration**	**Divide 24 hour dose* of current opioid (column 1) by relevant figure below to calculate initial 24 hour dose of new opioid and/or new route (column 2)**
Example 120 mg oral morphine in 24 hours	subcutaneous diamorphine	**Divide by 3** (120 mg / 3 = 40 mg subcutaneous diamorphine in 24 hours)
ORAL TO ORAL ROUTE CONVERSIONS		
oral codeine	oral morphine	**Divide by 10**
oral tramadol	oral morphine	**Divide by 5**
oral morphine	oral oxycodone	**Divide by 2**
oral morphine	oral hydromorphone	**Divide by 7.5**
ORAL TO TRANSDERMAL ROUTE CONVERSIONS		
oral morphine	transdermal fentanyl	*Refer to manufacturer's information***
oral morphine	transdermal buprenorphine	*Seek specialist palliative care advice*
ORAL TO SUBCUTANEOUS ROUTE CONVERSIONS		
oral morphine	subcutaneous morphine	**Divide by 2**
oral morphine	subcutaneous diamorphine	**Divide by 3**
oral oxycodone	subcutaneous morphine	**No change**
oral oxycodone	subcutaneous oxycodone	**Divide by 2**
oral oxycodone	subcutaneous diamorphine	**Divide by 1.5**
oral hydromorphone	subcutaneous hydromorphone	*Seek specialist palliative care advice*
OTHER ROUTE CONVERSIONS RARELY USED IN PALLIATIVE MEDICINE		
subcutaneous or intramuscular morphine	intravenous morphine	**No change**
intravenous morphine	oral morphine	**Multiply by 2**
oral morphine	intramuscular morphine	**Divide by 2**

* The same units must be used for both opioids or routes, eg mg morphine to mg oxycodone

** The conversion ratios of oral morphine:transdermal fentanyl specified by the manufacturer(s) vary from around 100:1 to 150:1 (*see Annex 2*)

7.6 CONTROL OF OPIOID-INDUCED NAUSEA AND VOMITING

Many opioid-naïve patients will develop nausea and/or vomiting when started on opioids. Tolerance in the majority of patients usually occurs within 5-10 days.

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

7.7 CONTROL OF OPIOID-INDUCED CONSTIPATION

SIGN 44

The majority of patients taking opioids for moderate to severe pain will develop constipation. Little or no tolerance develops. There remains uncertainty about the best management of constipation in this group of patients[206] although the best prophylactic treatment for preventing opioid-induced constipation is a combination of stimulant and softening laxatives.[207,208]

1++
3

8 Non-pharmacological treatment

8.1 COMPLEMENTARY THERAPIES

In this guideline complementary therapies are defined as the supportive methods used to complement the mainstream treatments for cancer pain. Although these therapies have increased in popularity, the evidence to support their use in the treatment of cancer pain remains weak.

Due to the small number and size of studies involved, individual results cannot be generalised to the population in this guideline. Each complementary therapy requires to be investigated separately. General themes that emerged were that any pain relief offered was of short duration but that patients found the experience a positive one.[209]

8.1.1 MASSAGE AND AROMATHERAPY

No evidence was identified that massage or aromatherapy reduce long term cancer pain.

One systematic review suggests that massage alone and aromatherapy with massage may confer short term benefits on psychological well-being.[210] Studies report a reduction in measures of anxiety of 19-32%. The evidence on the effect of these interventions on depression, pain relief or other physical symptoms was conflicting. | 1^{++}

An RCT published after the systematic review reported aromatherapy massage as a pleasurable experience for patients but it did not provide any long term pain relief.[209] | 1^{++}

One randomised cross-over study showed therapeutic massage to reduce pain and anxiety in the short term, but this effect did not persist after four weeks.[211] | 1^{++}

8.1.2 MUSIC THERAPY

A systematic review of the use of music to relieve pain showed considerable variation in the effect of music, and indicated statistical heterogeneity. The only patient group in which music was shown to produce a small but significant reduction in pain was in patients suffering from postoperative pain.[212] An RCT published after the systematic review showed that in individuals with non-malignant pain the use of music resulted in pain reductions of around 20% in experimental subjects compared to control subjects over a period of seven days.[213] | 1^{++} 1^{+}

8.1.3 ACUPUNCTURE

One systematic review considered evidence for acupuncture as an analgesic for patients with cancer pain.[214] It identified seven relevant studies, including a high quality RCT. The review concluded that there was no evidence to support the use of this technique for pain relief in cancer patients. | 2^{++}

One RCT was identified on the analgesic effects of auricular acupuncture in cancer pain. This showed that pain decreased by 36% in two months compared with a 2% decrease in the placebo group. The subjects had peripheral and central neuropathic pain and were on concurrent, steady analgesic therapy.[215] | 1^{++}

8.1.4 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

Transcutaneous electrical nerve stimulation (TENS) involves the introduction of pulses of low voltage electricity into tissue via electrodes placed on the skin for the relief of pain. Transcutaneous spinal electroanalgesia (TSE) involves the placement of electrodes over the spine and operates with pulses at a higher frequency and often higher voltage than TENS.

One RCT compared TENS, TSE and placebo for pain reduction and showed no significant differences between the two treatments and placebo using pain report alone.[216] | 1^{+}

8.1.5 REFLEXOLOGY

One RCT was identified where partners were taught to deliver reflexology to patients with pain due to metastatic cancer (42 experimental subjects and 44 control subjects with a pain score of 2 or greater on a 1-10 pain scale). A 34% reduction in pain from baseline was reported in the group receiving reflexology compared to a 2% reduction in the control group.[217] This study concluded that reflexology may be helpful in the management of cancer-related pain. Further studies are required to determine whether pain relief from this intervention can be maintained. | 1+

8.1.6 REIKI

One trial compared patients with advanced cancer and pain who received either an opioid and rest as the intervention or an opioid and reiki. The reiki group reported a small improvement in pain after one week.[218] Although the numbers are small and the study of short duration the results indicate that touch therapies may have a place in the management of cancer pain and further research is required. | 1+

8.1.7 HYPNOTHERAPY

Hypnotherapy has been shown to reduce treatment related pain and mucositis in patients with cancer.[219] | 2+

Two systematic reviews were identified which included studies of varying design addressing the use of hypnosis in managing cancer pain. The first included 27 studies (one RCT, one observational study, one retrospective questionnaire, 24 case studies, total n = 199).[220] One study reported significant reductions in physical distress scores for patients assigned hypnotherapy compared to control ($p < 0.01$). Another study (n = 8), had pain relief from hypnotherapy which resulted in reduced opioid analgesic requirements. All case studies reported improvements in pain after hypnotherapy. Interpretation of results is difficult as patient populations were not adequately described and the small numbers may not have power to detect meaningful differences. Validated measurement tools were only used in two studies. | 2++

The second systematic review included three RCTs on post surgical pain or oral mucositis.[221] Numbers are small and methodological details are scant. | 1-

There is insufficient evidence to make a recommendation. Further research with clearly defined aims and outcomes, using validated outcomes tools is indicated.

8.2 RADIOTHERAPY FOR RELIEVING PAIN IN PATIENTS WITH BONE METASTASES

SIGN 44

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.[115] | 1+

One systematic review of 11 RCTs for painful bone metastases found no difference in pain relief between single dose and fractionated radiotherapy (response rate for single fraction, 60% of 1,814 patients; response rate for multiple fractions, 59% of 1,807 patients; OR 1.03, 95% CI, 0.89 to 1.19).[222] There was also no difference in complete pain response rates for single fraction radiotherapy (34%) and multifraction radiotherapy (32%) with an OR of 1.11 (95% CI 0.94 to 1.30). Patients treated by single fraction radiotherapy had a higher re-treatment rate with 21.5% requiring re-treatment compared to 7.4% of patients in the multifraction radiotherapy arm (OR 3.44, 95% CI 2.67 to 4.43). The pathological fracture rate was also higher in single fraction radiotherapy arm patients. Three per cent of patients treated by single fraction radiotherapy developed pathological fracture compared to 1.6% for those treated by multifraction radiotherapy (OR 1.82, 95% CI 1.06 to 3.11). | 1++

Another systematic review showed no significant difference between response rates to pain for single and multiple fraction radiotherapy (23% complete response for single fraction radiotherapy and 24% complete response for multiple fraction radiotherapy). All radiotherapy was associated with improved mobility and acceptable side effects.[223] | 1+

One RCT was terminated early because of a lack of difference in the outcome between single and multiple fractionation.[224] 1+

A systematic review showed weak evidence of a small beneficial effect of radioisotopes for pain control in the short and medium term (one to six months), with no modification of analgesia use (NNT for pain relief = 4).[225] There was no evidence that radioisotopes modify the incidence of bone complications or mortality. There is no available evidence for the effect of radioisotopes on quality of life but a higher incidence of severe secondary effects such as leukocytopenia and thrombocytopenia has been observed (NNH for leukocytopenia =11). 1+

^{186}Re-HEDP was shown, in three RCTs involving small numbers, to relieve bone pain in patients with breast cancer,[226] provided good palliation of pain in lung cancer[227] and produced inconsistent results in patients with hormone refractory prostate cancer.[228] The availability of Rhenium treatment may be limited to specialist centres. 1++ 1+

Another systematic review of radioisotopes for relief of cancer pain reported no significant difference between ^{89}Sr (strontium) and other radioisotopes in terms of pain response rate or toxic effects.[229] 1+

B **All patients with pain from bone metastases which is proving difficult to control by pharmacological means should be referred to a clinical oncologist for consideration of external beam radiotherapy or radioisotope treatment.**

8.3 CEMENTOPLASTY

Percutaneous cementoplasty involves the injection of acrylic bone cement into malignant bone cavities in order to relieve pain or stabilise the bone, or both. Percutaneous vertebroplasty involves the injection of acrylic bone cement into the vertebral body in order to relieve pain and/or stabilise the fractured vertebrae and in some cases, restore vertebral height. Balloon kyphoplasty is an extension of the vertebroplasty technique that uses an inflatable bone tamp to restore the vertebral body towards its original height while creating a cavity to be filled with bone cement.[230] 4

Many patients with cancer present with osteolytic involvement of the spine which may cause loss of vertebral height. This is associated with significant morbidity and mortality. Most of these patients will have reduced mobility and back pain which may not be responsive to drug treatment. Medical, radiotherapeutic and surgical options may be inadequate or too invasive in these cases.

Case series of osteoporosis and cancer patients with vertebral loss of height, show consistently that vertebroplasty and kyphoplasty may provide sustained pain relief in those with metastatic bone pain which can last up to two years.[231-234] 3

The procedure appears safe, but all studies report technical incidents involving cement leakage, although clinical complications are rare.[235] These are reduced if kyphoplasty is used.[232] 3

Kyphoplasty is more time consuming and more often requires a general anaesthetic than vertebroplasty, which is an outpatient procedure under conscious sedation.

D **Patients with bone pain from malignant vertebral collapse proving difficult to control by pharmacological means should be referred for consideration of vertebroplasty where this technique is available.**

Case series have shown that good pain control and improved mobility can be achieved using the percutaneous injection of acrylic cement into acetabular or pelvic bones weakened by bone metastases.[236-238] The procedure requires a short period of hospitalisation, with few side effects. Rates of leakage of injected cement into surrounding tissues range from 6-50% however, symptomatic cases relating to cement leaks were only reported in 6-11% of cases.[236,238] 3

D **Patients with bone pain from pelvic bone metastases proving difficult to control by pharmacological means and reduced mobility should be considered for percutaneous cementoplasty.**

8.4 ANAESTHETIC INTERVENTIONS

Despite management by multidisciplinary teams according to the principles of the WHO ladder, up to 20% of cancer patients may have poorly controlled pain.[3,90] It is this group of patients who are most likely to benefit from some form of anaesthetic intervention. | 3

There is a limited amount of high quality evidence for anaesthetic techniques to manage cancer pain. Ten papers and two reviews were identified, of which the majority dealt with coeliac plexus block. Two papers looked at local anaesthetic used either via the epidural route or topically as part of pain control for breast cancer surgery. One paper looked at the effect of epidurals for major gynaecological surgery. Evidence for other anaesthetic interventions such as plexus or peripheral nerve blocks is limited to case series, case reports and expert opinion.

Four RCTs and two cohort studies of neurolytic coeliac plexus block (NCPB) compared either to placebo[239-241] or another intervention, such as splanchnic nerve block[242] or epidural butamben[243] were identified. Although there are design faults in all of these, the largest RCT does show analgesic benefit from NCPB, but no reduction in opioid consumption or improvement in survival.[241] | 1++
1+
1-
2-

Although in widespread use and accepted to be of benefit to some patients, there are very few high quality trials of neuraxial opioids. One large randomised multicentre study of intrathecal opioids delivered by an implantable drug delivery system, did show a benefit both in terms of analgesia and survival versus standard medical management.[244] A study comparing different intrathecal local anaesthetics in a mixed patient group (cancer and non-cancer) also found some benefit but there was no control arm.[245] | 1+
1-

A review of epidural, subarachnoid and intracerebroventricular (ICV) routes of opioid administration found limited high quality evidence but similar efficacy for all neuraxial routes, with a possibility that ICV may have a better opioid side effect profile.[246] | 4

One RCT examined the efficacy of topical anaesthesia in reducing postoperative pain in breast cancer patients.[247] Acute pain at rest and with movement did not differ between the anaesthesia and control groups, and the analgesics consumed during the first 24 hours were the same for both groups. However, time to the first analgesia requirement was longer ($p = 0.04$), and codeine and paracetamol consumption during the second to fifth days was less ($p = 0.001$, and $p = 0.004$, respectively) in the anaesthesia versus the control group. Three months postoperatively, pain in the chest wall, axilla, and the total incidence and the intensity of chronic pain were significantly less in the group who received topical anaesthesia ($p = 0.004$, $p = 0.025$, $p = 0.002$ and $p = 0.003$, respectively). | 1+

Another RCT of patients who underwent surgery for breast cancer showed that multimodal analgesia reduced acute and chronic pain.[248] The treatment group consumed less paracetamol postoperatively (469 versus 991 mg; $p < 0.002$) than the controls, exhibited lower VAS scores at rest in the post-anaesthesia care unit ($p = 0.001$) and on 1, 3, and 5 days postoperatively ($p = 0.040$, $p = 0.015$, and $p = 0.045$, respectively). Three and six months after surgery, 18 of 22 (82%) and 12 of 21 (57%) of the controls reported chronic pain versus 10 of 22 (45%) and 6 of 20 (30%) in the treatment group ($p = 0.028$ and $p = 0.424$, respectively); 5 of 22 and 4 of 21 of the controls required analgesics versus 0 of 22 and 0 of 20 of those treated ($p = 0.048$ and $p = 0.107$, respectively). | 1+

B **Interventions such as coeliac plexus block and neuraxial opioids should be considered to improve pain control and quality of life in patients with difficult to control cancer pain.**

☑ Any patient with difficult to control pain despite optimal management of systemic/ oral therapy should be assessed by an anaesthetist with expertise in pain medicine, for consideration of an appropriate intervention. Patients most likely to benefit include patients with significant locally advanced disease, neuropathic pain or marked movement-related pain.

9 Provision of information

9.1 PROVIDING INFORMATION

A patient version of this guideline is available from the SIGN website, **www.sign.ac.uk**

9.2 SOURCES OF FURTHER INFORMATION

Many cancer care centres and public libraries have access to the internet. While the internet can provide a vast range of information, patients should be advised to act cautiously as they may not have the means of determining the accuracy or reliability of a site. Healthcare professionals should guide patients to appropriate sites and advise patients that any information found on the internet should be discussed with members of their multidisciplinary team.

Cancerbackup Scotland
Suite 2, Third Floor, Cranston House 104/114 Argyle Street, Glasgow G2 8BH
Tel: 0141 223 7676/0808 800 1234 • Fax: 0141 248 8422
www.cancerbackup.org.uk

A free one to one service which provides counselling and emotional support for people with cancer and their families and friends. Produces over 50 booklets and a BACUP NEWS three times a year.

Cancer Help UK
www.cancerhelp.org.uk

CancerHelp UK is the patient information website of Cancer Research UK. It provides a free information service about cancer and care for people with cancer and their families. It includes specific information on cancer and pain control.

Cancer in Scotland
Scottish Executive Health Department, St Andrew's House, Regent Road
Edinburgh, EH1 3DG
Fax: 0131 244 2989
www.show.scot.nhs.uk/sehd/cancerinscotland/ • Email: Cancer@scotland.gsi.gov.uk

Cancer in Scotland identifies the wide range of actions necessary to prevent, detect and improve treatment and care for people with cancer in Scotland.

DIPEx (Database of individual experiences)
www.dipex.org

DIPEx is a website that reports on a wide variety of personal experiences of health and illness. People can watch, listen to or read interviews, find reliable information on treatment choices and where to find support. The site covers heart disease, epilepsy, screening programmes and cancers.

Healthyliving
Helpline: 0845 2 78 88 78
www.healthyliving.gov.uk

Promotes Scotland's healthy living programme and is designed to help people attain a healthier diet and a more active lifestyle by providing resources, advice and support on healthy eating and physical activity.

Macmillan Cancer Support (Scotland)
Osborne House, 1-5 Osborne Terrace, Edinburgh EH12 5HG
Tel: 0131 346 5346 • Fax: 0131 346 5347
www.macmillan.org.uk • Email: agow@macmillan.org.uk

The Scottish office of the UK charity, which supports people with cancer and their families with specialist information, treatment and care.

Maggie's Centres Scotland
Maggie's Dundee, Tom McDonald Avenue, Ninewells Hospital, Dundee DD2 1ZV
Tel: 01382 496 384
www.maggiescentres.org • Email: maggies.centre@ed.ac.uk

The aim of Maggie's Centres is to help people with cancer to be as healthy in mind and body as possible and enable them to make their own contribution to their medical treatment and recovery.

Maggie's Edinburgh, The Stables, Western General Hospital, Crewe Road South
Edinburgh EH4 2XU.
Tel: 0131 537 3131 • Fax: 0131 537 3130

Maggie's Glasgow, The Gatehouse, Western Infirmary, 10 Dumbarton Road
Glasgow G11 6PA
Tel: 0141 330 3311 • Fax: 0141 330 3363

Maggie's Highlands, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ
Tel: 01463 706306

Marie Curie Cancer Care (Scotland)
29 Albany Street, Edinburgh, EH1 3QN
Tel: 0131 456 3710 • Fax: 0131 456 3711
www.mariecurie.org.uk

Marie Curie Cancer Care, a comprehensive cancer care charity, provides practical nursing care at home and specialist multidisciplinary care through its ten Marie Curie Centres.

Pain Association Scotland
Cramond House, Cramond Glebe Road, Edinburgh, EH4 6NS
Tel: 0131 312 7955 • Freephone: 0800 783 6059 • Fax: 0131 312 6007
www.painassociation.com

The Pain Association Scotland is for all cancer patients suffering from pain and offers the opportunity for patients and their carers to join support groups.

Samaritans
The Upper Mill, Kingston Road, Ewell, Surrey, KT17 2AF
Tel: 020 8394 8300 • Helpline: 0845790 90 90 • Fax: 020 8394 8301
www.samaritans.org.uk • Email: admin@samaritans.org • Email: jo@samaritans.org
• Write to: Chris, P.O. Box 90, Stirling, FK8 2SA

Samaritans is available 24 hours a day to provide confidential emotional support for people who are experiencing feelings of distress or despair, including those which may lead to suicide.

10 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

10.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementing the recommendations made in the guideline. Where current practice will not change as a result of the recommendations it is unlikely there will be resource implications.

The group has identified two recommendations that will have additional resource implications for NHSScotland.

10.1.1 BISPHOSPHONATES

B **Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with metastatic bone disease.**

It is anticipated that this recommendation will result in a small increase in bisphosphonate prescribing.

10.1.2 CEMENTOPLASTY

D **Patients with bone pain from malignant vertebral collapse proving difficult to control by pharmacological means should be referred for consideration of vertebroplasty where this technique is available.**

There is limited availability of this procedure across NHSScotland. There are two procedures; cementoplasty on an outpatient basis, and kyphoplasty, which requires an anaesthetic. Both procedures are time consuming and will require radiological screening equipment and access to resuscitation equipment.

10.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following key points to audit to assist with the implementation of this guideline.

The proportion of patients:

- who receive screening for psychological distress.
- with distress and disability resulting from cancer pain who receive cognitive behaviour therapy.
- who receive education about the range of pain control interventions available to them.
- who receive a pain assessment.
- who have treatment outcomes monitored regularly using validated multidimensional pain assessment tools.
- with cognitive impairment who are assessed with self assessment pain scales.
- with cognitive impairment who cannot complete a self assessment scale who are assessed with an observational pain rating scale.
- in whom appropriate analgesia for breakthrough pain is prescribed.
- receiving NSAIDs who also are prescribed misoprostol 800 mcg/day, standard dose PPIs or double dose H2RAs.
- with metastatic bone disease who are prescribed bisphosphonates.
- with neuropathic pain who are prescribed either a tricyclic antidepressant or anticonvulsant.
- with severe pain who are commenced on oral morphine as first line therapy, unless the oral route is unavailable.
- with severe pain who are commenced on a subcutaneous opioid who receive diamorphine as first line therapy.
- with stable pain who are taking an oral opioid as a once or twice daily modified release preparation.
- with pain from bone metastases which is unrelieved by analgesics who are considered for external beam radiotherapy or radioisotope treatment.
- with bone pain from malignant vertebral collapse proving difficult to control by pharmacological means who are considered for vertebroplasty.
- with bone pain from pelvic bone metastastes proving difficult to control by pharmacological means and reduced mobility who are considered for percutaneous cementoplasty.

10.3 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium has issued guidance on the following medications.

Buprenorphine transdermal patches 5, 10 and 20 mcg/hour 7-day formulation (BuTrans®) are not recommended for use within NHS Scotland for the treatment of severe opioid responsive pain conditions, which are not adequately responding to non-opioid analgesics (August 2008).[249] This assessment is based on evidence involving elderly patients with osteoarthritic pain. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

Buprenorphine (Transtec®) patch is not recommended for use within NHS Scotland for the treatment of moderate to severe cancer pain and severe pain that does not respond to non-opioid analgesics (September 2004).[250]

Fentanyl transdermal patches (Durogesic®) are recommended for restricted use within NHSScotland (January 2003).[251] Transdermal fentanyl should be considered as a second-line alternative for patients with intractable pain due to non malignant conditions. It should be reserved for patients whose pain has initially been controlled by oral means, the pain being relatively stable. Its use should focus on such patients who have difficulty swallowing or have problems with opiate induced constipation.

Oxycodone (Oxynorm®) injection is accepted for restricted use within NHS Scotland only for the treatment of moderate to severe pain in patients with cancer (October 2004).[252]

Oxycodone prolonged release (OxyContin®) is accepted for restricted use within NHS Scotland for the treatment of severe non-malignant pain requiring a strong opioid analgesic (September 2005).[253]

Further information is available from the SMC website www.scottishmedicines.org.uk

11 The evidence base

11.1 SYSTEMATIC LITERATURE REVIEW

11.1.1 QUANTITATIVE SEARCH PARAMETERS

The literature review for this guideline addressed a set of key questions defined by the guideline development group *(see Annex 3)*. Searches were carried out for the period 1997 – June 2007. Databases used were the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, CINAHL, Embase, Medline, NEED, and PsycINFO. A search of key terms and key sites was also carried out on the Internet. A copy of the Medline version of the main strategy is available in the "Supporting materials" section of the SIGN website (www.sign.ac.uk/guidelines/published/support/index.html). Members of the guideline development group contributed additional literature.

The searches identified 2,570 papers of potential interest. Of these 386 were identified as having the potential to form part of the evidence base and were reviewed in detail.

Janssen-Cilag and Napp Pharmaceuticals were approached and provided information in relation to specific questions relating to opioid dosing and conversion ratios. This information is available for perusal on request to SIGN.

11.1.2 IDENTIFYING QUALITATIVE EVIDENCE

A literature search was carried out covering the databases CINAHL, Embase, Medline, and PsycINFO for the period 2000 to September 2006. This search focused on the identification of qualitative literature relevant to the experience of cancer pain. A copy of this search strategy is available in the "Supporting materials" section of the SIGN website (www.sign.ac.uk/guidelines/published/support/index.html).

The initial result from this search was 325 references. A sift of the results aimed at removing clearly irrelevant papers and focusing on research journals reduced this number to 224 references.

Two pairs of reviewers independently reviewed this list of abstracts to identify relevant papers reducing the number of relevant papers to 93. Only 28 of these papers were common to two pairs of reviewers.

Each pair of reviewers was then asked to identify themes that emerged from the joint list of selected papers, and to pick out papers that they thought represented the key issues underlying each theme. These papers were reviewed for methodological quality using the Critical Appraisals Skills Programme (CASP) checklist developed by the Public Health Resource Unit, Oxford. At the conclusion of this process nine papers are included as evidence, split into three themes: communication, existentialism, and relationships.

11.1.3 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to cancer pain. The search was run in Medline, Embase, CINAHL and PsycINFO, and the results were summarised and presented to the guideline development group for consideration when forming key questions that underpin the guideline.

The literature focused on themes including anxiety/depression, alternative treatments, barriers to pain management, breakthrough pain, care delivery, caregiver issues, communication, coping styles, health professional education, pain tools, patient beliefs, psychological issues, quality of life and symptom control. Many of these are addressed in either the narrative review or other sections of the guideline.

A copy of the Medline version of the patient search strategy is available in the "Supporting materials" section of the SIGN website (www.sign.ac.uk/guidelines/published/support/index html).

11.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- the relationship between cancer pain and associated levels of disability and distress.
- the psychosocial interventions that are effective in reducing the distress and disability associated with cancer pain.
- determining if the major component of patient distress is psychological or physical in nature.
- identifying educational strategies which will lead to both belief and behaviour change in healthcare professionals.
- determining the benefits and harms of moving directly from step 1 to step 3 in the WHO ladder in opioid-naïve patients with rapidly advancing pain.
- the use of bisphosphonates and risk of ONJ.
- determining the effect of paracetamol on pain and well-being in patients already on a strong opioid regimen.
- determining the balance of GI benefits and cardiovascular risks associated with COX-2 selective NSAIDs (eg celecoxib, etoricoxib and parecoxib).
- Complementary therapies - further research is needed into the effect on pain of each individual intervention; standardisation is required for the most appropriate research methods to carry this out.
- clarifying the role of eutectic mixture of local anaesthetics (EMLA) in chronic pain management.
- determining the role of ketamine as an adjuvant analgesic.
- determining the most effective dose of breakthrough analgesia for oral opioids by comparing doses that are a fixed proportion of the daily regular opioid with a dose titrated to the individual patient/pain.
- determining the appropriate titration process for hydrophilic opioids in the treatment of breakthrough pain.
- determining the role of opioids with different pharmacokinetic characteristics in the control of breakthrough pain.
- determining the role of lidocaine plasters in conditions other than postherpetic neuralgia.
- determining the side effects of different opioids using a systematic comparison.
- establishing the value of opioid switching.
- determining whether pregabalin is more effective than gabapentin in neuropathic pain control.
- determining the percentage increment that should be used when opioid doses are titrated upwards, and whether the increment varies at different dose ranges or with different opioids.
- determining the optimal use of cannabinoids for neuropathic pain.
- determining the effectiveness of reflexology, reiki and hypnotherapy in patients with cancer pain.

11.3 REVIEW AND UPDATING

This guideline was issued in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

12 Development of the guideline

12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. The views and interests of NHS Quality Improvement Scotland as the funding body have not influenced any aspect of guideline development, including the final recommendations. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

12.2 THE GUIDELINE DEVELOPMENT GROUP

Professor John Welsh *(Chair)*	*Professor of Palliative Medicine, Beatson Oncology Centre, Glasgow*
Dr Esther Murray	*Consultant Clinical Psychologist in Psychosocial Oncology, Ayrshire Central Hospital*
Dr Lesley Colvin	*Consultant Anaesthetist, Western General Hospital, Edinburgh*
Ms Marguerite Connolly	*District Nursing Sister, NHS Grampian*
Dr Paul Cormie	*MacMillan Lead General Practitioner (Cancer and Palliative Care), NHS Borders*
Dr David Craig	*Consultant Clinical Psychologist, Southern General Hospital, Glasgow*
Dr John Currie	*Consultant Anaesthetist, Royal Hospital for Sick Children, Glasgow*
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Dr Graeme Giles	*Consultant in Palliative Medicine, Strathcarron Hospice, Denny*
Mr Adam Gillespie	*Lay Representative, Glasgow*
Reverend Tom Gordon	*Chaplain, Marie Curie Hospice, Edinburgh*
Mr Robin Harbour	*Quality and Information Director, SIGN*
Dr Derek Jones	*Lecturer in Occupational Therapy, Queen Margaret University, Edinburgh*
Ms Linda Kerr	*Clinical Nurse Specialist in Palliative Care, Ayr Hospital*
Ms Alison MacRobbie	*Palliative/Community Care Pharmacist, NHS Highland*
Ms Jane Mair	*Community Cancer Support Nurse, Inverurie*
Dr Moray Nairn	*Programme Manager, SIGN*
Dr Kathleen Sherry	*Consultant in Palliative Medicine, The Ayrshire Hospice, Ayr*
Ms Janet Trundle	*Macmillan Specialist Pharmacist in Palliative Care, NHS Greater Glasgow and Clyde*
Ms Gillian Wilson	*Lay Representative, Dunbar*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

12.2.1 PATIENT INVOLVEMENT

In addition to the identification of relevant patient issues from a broad literature search, SIGN involves patients and carers throughout the guideline development process in several ways. SIGN recruits a minimum of two patient representatives to guideline development groups by inviting nominations from the relevant "umbrella", national and/or local patient focused organisations in Scotland. Where organisations are unable to nominate, patient representatives are sought via other means, eg from consultation with health board public involvement staff.

Further patient and public participation in guideline development was achieved by involving patients, carers and voluntary organisation representatives at the National Open Meeting (*see section 12.4.1*). Patient representatives were invited to take part in the peer review stage of the guideline and specific guidance for lay reviewers was circulated. Members of the SIGN patient network were also invited to comment on the draft guideline section on provision of information.

12.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Dr Susan Chater	*Consultant in Palliative Care, Edinburgh Cancer Centre, Western General Hospital, Edinburgh*
Ms Pat Hamilton	*Social Worker, Beatson Oncology Centre, Glasgow (deceased)*
Mr Ron Russell	*Lay Representative, Glenrothes*

12.4 CONSULTATION AND PEER REVIEW

12.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 23 April 2007 and was attended by 203 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

12.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr James Adams	*Consultant Physician in Palliative Medicine, Marie Curie Hospice and Glasgow Royal Infirmary*
Dr Tim Benton	*Medical Director, St Columba's Hospice, Edinburgh*
Dr Kirsty Boyd	*Consultant in Palliative Medicine, Royal Infirmary of Edinburgh*
Dr Jane Bray	*Specialist Registrar Public Health, Deaconess House, Edinburgh*
Dr Rodney Burnham	*Registrar, Royal College of Physicians, London*
Cancer genetics subgroup	*Scottish Cancer Group, Edinburgh*
Mr Robert Carachi	*Consultant Surgeon, Royal Hospital for Sick Children, Glasgow*
Rev Stuart Coates	*Chaplain, Strathcarron Hospice*
Ms Anne Davenport	*Palliative Care Pharmacist, Strathcarron Hospice, Denny*
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Ms Margaret Doherty	*District Nurse, Paisley*
Dr Colin Geddes	*Consultant Nephrologist, Western Infirmary, Glasgow*
Dr Belinda Hacking	*Consultant Clinical Psychologist and Head of Service, Edinburgh Cancer Centre*
Mr Joe Harrison	*Palliative Care Pharmacist, The Beatson West of Scotland Cancer Centre*
Ms Linda Johnstone	*Macmillan Area Lead Pharmacist Palliative Care, NHS Lanarkshire*
Dr Ewan Kelly	*Chaplain, St Columba's Hospice and Lecturer in Practical Theology, University of Edinburgh*
Dr Martin Leiper	*Consultant in Palliative Medicine, Roxburghe House, Royal Victoria Hospital, Dundee*
Rev David Mitchell	*Lecturer and practitioner in palliative care, West Cowal Manse, Tighnabruaich*
Dr William O'Neill	*GP Lead, Cancer & Palliative Care, Lothian Chair, Scottish Primary Care Cancer Group*
Dr David Oxenham	*Consultant in Palliative Medicine, Marie Curie Hospice*
Dr Helen Patterson	*Consultant Oncologist, Addenbrooke's Hospital, Cambridge*
Ms Elaine Peace	*Macmillan Nurse Consultant in Cancer and Palliative Care, Borders General Hospital, Melrose*
Professor Jon Raphael	*Consultant in Pain Medicine, Russells Hall Hospital, Dudley and Council Member, British Pain Society*
Rev Ian Stirling	*The Ayrshire Hospice, Ayr*
Ms Evelyn Thomson	*Regional Cancer Co-ordinator, West of Scotland Cancer Network, Dalian House, Glasgow*
Dr Adrian Tookman	*Medical Director, Marie Curie Hospice, Hampstead*
Ms Marylyn Wilson	*District Nursing Sister, Renfrewshire Community Health Partnership, Renfrew*

12.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Dr Keith Brown	*Chair of SIGN; Co-Editor*
Mrs Fiona McMillan	*Royal Pharmaceutical Society of Great Britain*
Dr Safia Qureshi	*SIGN Programme Director; Co-Editor*
Dr Graeme Simpson	*Royal College of Physicians of Edinburgh*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ATC	around the clock
BNF	British National Formulary
CASP	Critical Appraisals Skills Programme
CBT	cognitive behaviour therapy
CI	confidence interval
COX-2	cyclooxygenase-2
EDR	equianalgesic dose ratio
EMEA	European Agency for the Evaluation of Medicinal Products
EMLA	eutectic mixture of local anaesthetics
GI	gastrointestinal
GP	general practitioner
H2RA	histamine-2 receptor antagonists
HIV	human immunodeficiency virus
HR	hazard ratio
ICV	intracerebroventricular
IV	intravenous
MI	myocardial infarction
MSIR	immediate release morphine sulphate
MTA	multiple technology appraisal
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
NCPB	neurolytic coeliac plexus block
NHSQIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NNH	number needed to harm
NNT	number needed to treat
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
ONJ	osteonecrosis of the jaw
OR	odds ratio
OTFC	oral transmucosal fentanyl citrate
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PID	pain intensity differences
PPI	proton pump inhibitor
RCT	randomised controlled trial
rESS	revised Edmonton Staging System

RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
Sr	strontium
TENS	transcutaneous electrical nerve stimulation
THC	delta-9-tetrahydrocannabinol
TSE	transcutaneous spinal electroanalgesia
VAS	visual analogue scale
VRS	verbal rating scale
WHO	World Health Organization

Annex 1

Drug mixture 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 quantity for each drug in a specified volume in each syringe size is given. Provided the quantity 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 quantities stated the solution is either unstable or has not been tested and it is not possible to say whether it is stable or not.

Depending on the type of infusion device being used, the maximum volume which will fit into each size of syringe will vary, and the maximum quantities of individual drugs which can be mixed will therefore vary accordingly.

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 by specialist palliative care units. 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 palliative care specialists.

Combinations with dexamethasone have not been included. Since dexamethasone has a long duration of action, it is generally considered best practice to give it as a single daily bolus dose, preferably in the morning. High doses may require to be given in divided doses. Dexamethasone frequently causes compatibility problems, and if it is necessary to add it to subcutaneous infusions, it should be added last once the other drugs have been diluted as much as possible.[13]

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

The following combinations are not stable:

- diamorphine, dexamethasone and levomepromazine[254]
- diamorphine, cyclizine and metoclopramide (incompatibility depends on drug concentrations). This is not normally a rational combination from a clinical perspective.[255]
- cyclizine and hyoscine butylbromide (concentration dependent)[255]
- oxycodone and cyclizine (concentration dependent but incompatible at usual therapeutic doses of cyclizine).[256]

COMBINATIONS WITH DIAMORPHINE

Two drug combinations for subcutaneous infusion which are stable for 24 hours
Note: figures in this table are NOT clinical doses, and some of the figures are in excess of doses normally used clinically

Diluent: Water for Injections BP

Drug combination	Maximum quantity (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[251]	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 amounts then likely to get precipitate* **Maximum recommended daily dose 150mg*
Diamorphine and Haloperidol[251]	800 24	400 32	-	-	-	-	*If exceed these amounts then likely to get precipitate*
Diamorphine and Hyoscine Hydrobromide[252]	1200 3.2		-		-		-
Diamorphine and Hyoscine Butylbromide *(Buscopan)*[252]	1200 160		-		-		-
Diamorphine and Ketorolac[253]	47 40		82 74		90 90		-
Diamorphine and Levomepromazine *(Nozinan)*[248]	400 80		700 140		850 170		*Mixture can be irritant, dilute to largest possible volume*
Diamorphine and Metoclopramide[252]	1200 40		2100 70		2550 85		*Mixture can be irritant, dilute to largest possible volume*
Diamorphine and Midazolam[254]	266 40		466 70		566 85		-
Diamorphine and Octreotide[255]	100 0.9	200 0.6	175 1.5	350 1	212 1.9	425 1.2	-
Diamorphine and Ondansetron[256]	40 5		70 9		85 11		-

COMBINATIONS WITH DIAMORPHINE (CONTD)

Three drug combinations for subcutaneous infusion which are stable for 24 hours
Note: figures in this table are NOT clinical doses, and some of the figures are in excess of doses normally used clinically

Diluent: Water for Injections BP

Drug combination	Maximum quantity (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**[251]	160 160 16	280 280 28	340 340 34	*Above these amounts the mixture is likely to precipitate*
Diamorphine **and** **Haloperidol** **and** **Midazolam**[257]	560 4 32	980 7 56	1190 8.5 68	-
Diamorphine **and** **Levomepromazine** **and** **Metoclopramide**[258]	400 80 24	700 140 42	850 170 51	-

COMBINATIONS WITH OXYCODONE

Two drug combinations for subcutaneous infusion which are stable for 24 hours
Note: figures in this table are NOT clinical doses, and some of the figures are in excess of doses normally used clinically

Diluent: Water for Injections BP

Drug combination	Maximum quantity (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**	
Oxycodone and Cyclizine[250]	Incompatible at usual therapeutic doses of cyclizine			Do not mix if cyclizine concentration exceeds 3 mg/ml
Oxycodone and Haloperidol[250]	69 5	121 9	147 11	See note*
Oxycodone and Hyoscine Butylbromide (Buscopan)[250]	69 20	121 36	147 44	See note*
Oxycodone and Hyoscine Hydrobromide[250]	61 0.7	107 1.2	130 1.5	See note*
Oxycodone and Levomepromazine[250]	57 57	100 100	121 121	See note*
Oxycodone and Metoclopramide[250]	40 20	70 35	85 42	See note*
Oxycodone and Midazolam[250]	40 20	70 35	85 42	See note*

* Note: when 24 hour dose of oxycodone exceeds 60 mg, the volume of oxycodone injection required for breakthrough will be greater than 1 ml, and alternatives may need to be considered.

Annex 2

Conversion doses from oral morphine to transdermal fentanyl

Oral 24-hour morphine (mg/day)	Transdermal fentanyl (mcg/h)
< 90	25
90 – 134	37 (if available, otherwise 25)
135 – 189	50
190 – 224	62 (if available, otherwise 50)
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

Annex 3

Key questions used to develop the guideline

Adult or adolescent (age 12+) patients suffering pain due to cancer or associated with treatment of cancer. General neuropathic pain is excluded except in circumstances where pain mechanisms are shared with cancer pain.

PAIN ASSESSMENT	
Key question	**See guideline section**
1. Is there any evidence that diagnosis of pain type influences treatment?	4.2
2. Is there any evidence that daily pain assessment is more useful than weekly or other frequency of assessment in helping to control pain?	4.4.3
PSYCHOSOCIAL ISSUES	
Key question	**See guideline section**
3. Is there any evidence that would help identify predictors of cancer pain related distress and/or disability?	3.1.1
4. Is there any evidence supporting the use of cognitive behavioural therapy rather than other psychotherapeutic approaches to reducing disability and distress in patients suffering cancer pain?	3.1.2
5. Is there any evidence that treatment of anxiety or depression in cancer pain patients improves outcome?	3.1.2
6. Is there any evidence supporting specific psychological factors as predictors of adherence to treatments for cancer pain?	3.2
7. Is there any evidence that education of patients and/or health care professionals is effective in changing health beliefs in relation to cancer pain treatments?	3.2.1
NON-PHARMACOLOGICAL TREATMENTS	
Key question	**See guideline section**
8. What evidence is there of efficacy for complementary therapies in the treatment of cancer pain?	8.1
9. What evidence is there of the efficacy of radiotherapy in controlling cancer pain?	8.2
10. What evidence is there of the efficacy of vertebroplasty in controlling cancer pain?	8.3

PHARMACOLOGICAL TREATMENTS (NON-OPIOID DRUGS)	
Key question	**See guideline section**
11. Which non-opioid drugs have been shown to be effective in the treatment of cancer pain?	6.1, 6.2, 6.3, 6.4, 6.5, 6.6
12. What evidence is there to identify the best gastroprotective drugs to be prescribed along with NSAIDs?	6.1.1
13. What evidence is there for the efficacy of bisphosphonates in reducing bone events and in reducing bone pain in specific cancers?	6.2
14. Is there any evidence of effectiveness of cannabinoids in the control of cancer related pain?	6.6
15. Is there any evidence for the effectiveness of anaesthetic interventions for control of cancer pain?	8.4

PHARMACOLOGICAL TREATMENTS (OPIOID DRUGS)	
Key question	**See guideline section**
16. What is the evidence for conversion ratios between different opioids?	7.5
17. What evidence is there that opioid switching can improve pain control/reduce side effects?	7.4
18. What evidence is there of equivalence in analgesic effect and pharmacokinetics between fentanyl gel filled patches and fentanyl matrix patches?	7.1.2
19. Is there any evidence to support the use of buprenorphine in cancer pain?	7.1.6
20. What evidence is there for the efficacy of different opioids used in cancer patients with renal impairment who are (a) on dialysis, or (b) not on dialysis with respect to pain control and side effects?	7.1.6
21. What is the evidence for the current conversion ratios used when converting from one route of opioid administration to another?	7.2.3
22. What is the evidence that supports the current practice of reducing the dose of the new opioid by one third when converting from one opioid to another?	7.5
23. What is the optimum choice/dose/timing/route of administration of short acting opioid to provide effective analgesia for incident pain	7.1.4
24. What is the evidence for the dose of opioid (compared to background dose) used in control of breakthrough pain?	7.1.4
25. Which is the best choice of opioid used for breakthrough pain relief compared to the opioid used for maintenance pain relief to achieve maximal effective analgesia for cancer pain. (ie if morphine is used for maintenance analgesia, should it be morphine for breakthrough analgesia or another opioid)?	7.1.4
26. What is the evidence supporting the recommendation of different antiemetics in the control of opioid induced nausea and vomiting?	7.6
27. What is the evidence supporting the recommendation of different laxatives in the control of opioid induced constipation?	7.7
28. Is there any evidence that the route or schedule of administration of opioids influences the efficacy of treatment?	7.2.1, 7.2.2

PHARMACOLOGICAL TREATMENTS (OPIOID DRUGS)	
Key question	**See guideline section**
29. Which combinations of diamorphine and a) one or; b) two other drug(s) have evidence of compatibility/incompatibility over 24 hours?	7.2.1, Annex 1
30. Which combinations of oxycodone and a) one or; b) two other drug(s) have evidence of compatibility/incompatibility over 24 hours?	7.2.1, Annex 1
31. When opioid doses are titrated upwards, is there evidence for the percentage increment which should be used? If so, does the percentage increment vary at different dose ranges, or with different opioids?	7.3
32. What evidence is there to support the use of topical opioids for the control of local pain?	6.5.1

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