NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

Tús Áite do Shábháilteacht Othar
Patient Safety First

# Pharmacological Management of Cancer Pain in Adults

## National Clinical Guideline No. 9

An Roinn Sláinte
DEPARTMENT OF HEALTH

November 2015

**Guideline Development Group**
The Pharmacological Management of Cancer Pain in Adults Guideline was developed by a subgroup of the Health Service Executive (HSE)/Royal College of Physicians (RCPI) National Clinical Programme for Palliative Care. The Core Guideline Development Group was supported by a group of senior multidisciplinary service leads assembled by the National Clinical Programme for Palliative Care who evaluated the quality of the development process and documentation at key timepoints. This group was called the Guideline Steering Group.







**Using this National Clinical Guideline**
This guideline applies to healthcare professionals involved in the management of cancer pain. This includes Palliative Care staff, Physicians, Surgeons, General Practitioners, Pharmacists and Nursing staff in hospital, hospice and community-based settings. They may also be of interest to patients with cancer pain and their carers. This guideline does not apply to cancer survivors, to patients who do not have a cancer diagnosis or to other forms of acute or chronic non-malignant pain. This guideline does not apply to children.

The National Clinical Guideline and the summary National Clinical Guideline are available on the websites www.health.gov.ie/patient-safety/ncec and www.hse.ie/palliativecareprogramme.

The clinical burden of cancer pain is significant. Despite the advances in the management of pain since the first publication of the WHO cancer pain guidelines in 1986, there is evidence that there are significant variations in the success rates of its management. The increasing number of cancer survivors who live to an advanced age means that it is of paramount importance to reduce the prevalence of pain. The expected outcome of this guideline is to reduce cancer patient's pain and to improve their quality of life. The National Clinical Programme for Palliative Care has developed National Clinical Guideline Number 10 for Management of Constipation in Adult Patients Receiving Palliative Care which complements this guideline.

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## National Clinical Effectiveness Committee (NCEC)

The National Clinical Effectiveness Committee (NCEC) is a Ministerial committee established as part of the Patient Safety First Initiative. The NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

National Clinical Guidelines are "systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and service users' decisions about appropriate healthcare for specific clinical circumstances across the entire clinical system". The implementation of clinical guidelines can improve health outcomes, reduce variation in practice and improve the quality of clinical decisions.

The aim of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence based and consistent care across Irish healthcare services.

The oversight of the National Framework for Clinical Effectiveness is provided by the National Clinical Effectiveness Committee (NCEC). The NCEC is a partnership between key stakeholders in patient safety and its Terms of Reference are to:

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

It is recognised that the health system as a whole, is likely to be able to effectively implement and monitor only a small number of new national clinical guidelines each year. Not all clinical guidelines will be submitted for national endorsement and clinical guideline development groups can continue to develop clinical guidelines using an evidence based methodology in response to the needs of their own organisations.

Information on the NCEC and endorsed National Clinical Guidelines is available at:
www.health.gov.ie/patient-safety/ncec

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**Disclaimer**

The Guideline Development Group's expectation is that healthcare staff will use clinical judgement, medical, nursing and clinical knowledge in applying the general principles and recommendations contained in this document. Recommendations may not be appropriate in all circumstances and the decision to adopt specific recommendations should be made by the practitioner taking into account the individual circumstances presented by each patient/ resident and available resources.

Therapeutic options should be discussed with the responsible physician on a case-by-case basis as necessary.

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# 1 Background

## 1 Grading of recommendations

### *1.1.1 Key to grading method used to highlight quality of evidence and recommendations:*

This guideline uses a system for grading the quality of evidence based on the CEBM (Centre for Evidence Based Medicine) method of Oxford University(1) as follows:

- Level 1a Meta analyses of randomised control trials (RCT)
- Level 1b At least one RCT
- Level 2a At least one well designed controlled study without randomisation or systematic review (SR) of cohort studies
- Level 2b A well designed cohort study
- Level 3 Well designed experimental descriptive studies, such as case control or cross sectional studies
- Level 4 Case series
- Level 5 Expert Committee/Clinical experience

#### *1.1.1.1 Grading the strength of recommendations:*

- A Level 1 studies
- B Level 2 or 3 studies
- C Level 4 studies
- D Level 5 studies or inconsistent or inconclusive studies of any level

#### *1.1.1.2 Considered judgement:*

The Scottish Intercollegiate Guideline Network (SIGN) introduced the concept of considered judgement when formulating evidence based recommendations for SIGN 50 (2). Through the 'considered judgement' process, guideline developers are able to downgrade a recommendation where they consider there are important inconsistencies in the evidence base; evidence is not generalisable; not directly applicable to the target population; or for other reasons is perceived as being weaker than a simple evaluation of the methodology would suggest (3). As such, the recommendations made are a reflection of both the strength of the evidence informing the recommendation, but also the development group's decision as to the strength of recommendation that can be made based on that evidence.

## 1.2 Need for the National Clinical Guideline: Pharmacological Management of Cancer Pain in Adults

### *1.2.1 Clinical burden*

The clinical burden of cancer pain is significant. A large systematic review and meta-analysis of studies performed on articles relating to the prevalence of cancer pain over the past forty years was published by Van den Beuken-van Everdingen et al in 2007 (4). This found that pain was highly prevalent in cancer patients: 64% in patients with metastatic or advanced stage disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment. More than one-third of the patients with pain in the reviewed articles graded their pain as moderate or severe. This highlighted that, despite the clear WHO recommendations, cancer pain still is a major problem. The increasing number of cancer survivors who live to an advanced age means that it is of paramount importance to reduce the prevalence of pain at all stages of the disease process (4). The production of this guideline aims to inform, aid, and support health care professionals challenged with treating patients suffering from cancer-related pain.

### *1.2.2 Variation in practice and potential for improved health*

Despite the advances in the management of pain since the first publication of the WHO cancer pain guidelines in 1986, there is evidence that there are significant variations in the success rates of its management. Zech et al (1995) published the results of a ten year prospective study of 2,226 cancer patients in Germany and found that 88% received good or satisfactory pain relief (5). However, in the same year, a multicentre study in France of analgesic therapy in a cancer setting found that 51% of patients still reported inadequate pain relief following treatment (6). More recently, Cascinu et al (2003) performed a prospective study of 120 patients with advanced cancer admitted to an oncology service in Italy, and found that 43% of patients had inadequate analgesia (7). These international variations in practice also highlight the potential for improved health outcomes and quality of life associated with evidence-based guidelines that have been developed specifically for the healthcare service and context in which they are to be applied. One of the reasons for this is because pain often affects and augments other symptoms that cancer patients suffer. Moreover, studies demonstrate a significant correlation between pain, depression, fatigue and other symptoms commonly seen in a cancer setting; these are known as 'symptom clusters'(8). In essence, the potential improvements in health and symptom outcomes, and therefore quality of life outcomes, for cancer patients may be greater than those gained by the reduction of their pain alone. In order to successfully adopt best practices, the standardisation of care processes is critical. The use of education and skills development programs are vital for the spread of best practices, as well as the acceleration of their use (9). The development of this guideline aims to aid this process in the Irish context.

## 1.3 Aim of National Clinical Guideline

The purpose of the National Clinical Guideline is to provide recommendations based on best available evidence for the pharmacological treatment of cancer pain in adults. The aim is to benefit patients suffering with cancer pain. The expected outcome of the treatment as highlighted by this guideline is to reduce a cancer patient's pain and improve their quality of life.

## 1.4 Scope of National Clinical Guideline, target population and target audience

The National Clinical Guideline applies to healthcare professionals involved in the management of cancer pain. This includes Palliative Care staff, Physicians, Surgeons, General Practitioners, Pharmacists and Nursing staff in hospital, hospice and community-based settings. The guideline recommendations indicate where specialist advice should be sought.

The Guideline will also be of interest to patients with cancer pain and their carers. A patient information leaflet can be accessed on the National Clinical Programme for Palliative Care Website http://www.hse.ie/palliativecareprogramme and the www.health.gov.ie/patient-safety/ncec.

The National Clinical Guideline does not apply to cancer survivors, to patients who do not have a cancer diagnosis or to other forms of acute or chronic non-malignant pain. The National Clinical Guideline does not apply to children.

## 1.5 Legislation and other related policies

In palliative care practice, up to a quarter of all prescriptions written are for licensed drugs given for unlicensed indications, and/or via an unlicensed route (10-12). Often it is simply a matter of the route or dose being different from those in the manufacturer's SPC (summary of product characteristics). It is important to recognise that the licensing process for drugs regulates the marketing activities of pharmaceutical companies, and not prescribing practice. Unlicensed use of drugs by prescribers is often appropriate and guided by clinical judgment. This practice is safeguarded in legislation in accordance with Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I 540/2007) as amended. Furthermore, drugs prescribed outside license can be dispensed by pharmacists and administered by nurses or midwives (13).

## 1.6 Roles and responsibilities

It is the role of line managers to ensure that healthcare staff are aware of these guidelines (14). It is also the role of line managers to ensure that training is available for staff where necessary to ensure that staff possess an appropriate level of palliative care competence and knowledge (Palliative Care Competence Framework, 2014 (15)) to put this guideline into practice.

Each health professional/healthcare provider is accountable for their practice. This means being answerable for decisions he/she makes and being prepared to make explicit the rationale for those decisions, and justify them in the context of legislation, case law, professional standards and guidelines, evidence-based practice, professional and ethical conduct. All healthcare staff providing care to adult patients with cancer pain in hospital, hospice and community-based settings should:

- comply with this National Clinical Guideline and related policies, procedures and protocols;
- adhere to their code of conduct and scope of practice guidelines as appropriate to their role and responsibilities;
- maintain competence in the management of cancer pain in adult patients;
- in using this guideline be aware of the role of appropriate delegation and referral to specialists when necessary.

The recommendations in this guideline are intended to serve as part of the evidence-based process, which relies on a combination of recommendations based on best research evidence, the clinical state and circumstances, the patient's preferences and actions, and also clinical expertise. Use of this guideline in isolation without due consideration of these other parameters may result in a sub-optimal outcome for the patient. Clinical decision making in the management of cancer pain in adults should be clearly documented.

## 1.7 Guideline Development Group

### *1.7.1 Guideline Development Group*

The Guideline Development Group (GDG) comprised of core working members who carried out the work involved in developing the guideline. Additional members of the guideline

development group, senior multidisciplinary service leads assembled by the National Clinical Programme for Palliative Care and known as the Guideline Steering Group, evaluated the quality of the development process and documentation at key stages of the process as outlined in Appendix I.

### *1.7.2 Conflict of interest*

The members of the GDG were required to complete a conflict of interest form at the initial outset of the consultation process of this guideline. No conflicts of interest were identified.

### *1.7.3 Funding and editorial independence*

This was an independently produced guideline. There was no external funding, commercial input or resource provided for this guideline by any service or organisation, and as such no potential for influence on editorial independence.

## 1.8 Methodology and literature review

### *1.8.1 The ADAPTE Collaboration*

The ADAPTE Collaboration (16) is an international collaboration of researchers, guideline developers, and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines. This group's main endeavor is to develop and validate a generic adaptation process that will foster valid and high-quality adapted guidelines as well as the users' sense of ownership of the adapted guideline.

The method for this guideline development follows the principles of ADAPTE tool for guideline adaptation (16). Guideline adaptation is the systematic approach to the endorsement and/or modification of a guideline(s) produced in one cultural and organisational setting for application in a different context. Adaptation may be used as an alternative to the de-novo guideline development, for example, for the customising of an existing guideline or guidelines to suit the local context.

A summary of the adaptation process is given in Appendix II.

### *1.8.2 Existing guidelines*

There are a number of international guidelines in the area of cancer-related pain. A formal literature search was undertaken by a healthcare provider librarian to identify cancer pain guidelines published between November 2008 and November 2011 (the time of commencement of document preparation). The identified guidelines were graded for methodological rigour according to the AGREE II tool (17). A copy of these scores is available in Appendix III.

The AGREE instrument is a tool that assesses the methodological rigour and transparency with which a guideline is developed. It is used internationally and forms part of the ADAPTE process. Using this tool, the SIGN guideline was found to be of the highest methodological rigour, whilst three further guidelines were additionally selected for inclusion as part of the development process of this guideline (see below).

### *1.8.3 The SIGN Guideline*

The Scottish Intercollegiate Guidelines Network (SIGN) (2) develops evidence-based clinical practice guidelines for the National Health Service (NHS) in Scotland. SIGN guidelines are

derived from a systematic review of the scientific literature and are designed as a vehicle for accelerating the translation of new knowledge into action to meet the aim of reducing variations in practice, and improving patient-important outcomes (2). In November 2008, SIGN published guidelines for the management of cancer pain. These comprehensive guidelines were considered by the development group to represent the most rigorous and complete recommendations on the management of cancer pain, based on best systematic evidence (up to the date of their publication). The SIGN 106 cancer pain guideline was thus identified as a baseline for this national cancer pain guideline. There were no plans to update the SIGN Guideline 106 Control of Pain in Adults with Cancer, as of 28th November 2014.

### *1.8.4 Additional source guidelines*

Guidelines that were considered most suitable for inclusion as additional sources of updated information were:

- The National Comprehensive Cancer Network guidelines (2010) (18)
- Palliative Adult Network Guidelines third edition (2011) (19)
- Oncology Nursing Society (2009) (20)

The GDG assessed the guidelines for consistency, acceptability, and applicability of recommendations. In meeting an acceptable standard of rigour, as identified through the AGREE II tool scoring process, the development group thus deemed these guidelines as being of an acceptable standard to directly refer to in this adapted guideline. This means these source guidelines may be directly referenced in this document, without a requirement to cite a primary evidence source.

A recommendation matrix table was constructed based on the most consistent themes between the source guidelines. This table was then used as a resource by the development group for consideration when formulating recommendations (see Appendix IV).

### *1.8.5 Health questions*

In parallel with the above guideline search process, health questions were formulated individually by the core GDG members, and then refined by the wider group. The health questions highlight key areas of importance to clinicians and patients and reflect areas where further clarification and knowledge is required. A list of the health questions is available in Appendix V. For each health question, a formal systematic literature search of key databases was performed (see below). Additionally, the health questions and subsequent literature searches would investigate important areas where additional evidence may have become available since the publication of the SIGN guideline in 2008.

### *1.8.6 Literature searches: health questions*

Once health questions were identified, the process of identifying updated literature commenced. The European Palliative Care Research Collaborative (EPCRC, 2006-2010) performed a number of high level systematic reviews so as to inform the 2012 EAPC Cancer Pain Guidelines (21, 22). These systematic reviews were published in July 2011. The EPCRC searches were of high quality and any health questions that were addressed in these systematic reviews were not undertaken by the development group (21). Of the 40 health questions identified by the development group, 18 were addressed by the EPCRC searches, which left 22 health questions for investigation.

The GDG then undertook literature searches on each of these health questions for the period between June 2007 and November 2011. June 2007 is when the SIGN guideline development team (2) completed their literature searches, and was therefore considered an appropriate starting point for the new searches. Databases used were the Cochrane Database of Systematic

Reviews, Cochrane Controlled Trials Register, CINAHL, Medline, and PsycINFO. A search of key terms and key sites was also carried out on the Internet. Due to the time lapse between completion of guideline and signoff, a second literature search using the databases listed above was undertaken in January 2015, for the time period 2011 to December 2014 to ensure currency of the document. A sample search diagram is included in Appendix VI. A summary of the searches is available in Appendix VII.

### *1.8.7 Reviewing the evidence and consensus techniques.*

After the literature searches were completed, the resulting search abstracts were reviewed by the working group members over a number of meetings. Abstracts that were clearly not eligible for inclusion were excluded, and then the suitable articles were reviewed in their entirety by two members of the group who were not involved in the primary search (independent reviewers). The final relevant articles were identified and included for consideration in the formulation of the guideline recommendations, and their levels of evidence recorded in the final document.

### *1.8.8 Guideline development process - in conclusion*

Recommendations that are made in this guideline reflect the best evidence from the SIGN (2), PANG (19), NCCN (18) and Oncology Nursing Society (20) guidelines, as well as the independent searches performed on each of these guideline recommendations performed by the development group and in conjunction with the literature searches performed by the working group on the additionally derived health questions.

Initially, it was decided that if there were any significant issues relating to the formation of a consensus a value-based consensus decision-making model would be employed (23). However, there were no significant consensus issues identified by the Chair throughout the process and any areas of discussion were resolved informally without the use of this model being necessary.

## 1.9 External review

The GDG is very grateful to the two international experts who reviewed the guideline: Professor Peter G Lawlor, Associate Professor, Division of Palliative Care, Department of Medicine, University of Ottawa, Clinical Investigator, Bruyère and Ottawa Hospital Research Institutes, Medical Director, Palliative Care Unit, Bruyère Continuing Care and Professor Mike Bennett, St Gemma's Professor of Palliative Medicine, Consultant in Palliative Medicine, St Gemma's Hospice, Leeds, England. The external reviewers commended the guideline for comprehensively covering the common issues encountered in management of cancer pain. The GDG carefully considered the advice and comments received and made amendments to the guideline as appropriate. A thematic summary of the external review and amendments to guideline is included in Appendix VIII.

## 1.10 Implementation of National Clinical Guideline

### *1.10.1 Dissemination*

The National Clinical Programme for Palliative Care Working Group and the guideline development group will take responsibility for guideline dissemination through the following actions:

- The National Clinical Guideline, Summary National Clinical Guideline, quick reference guides and patient information leaflet will be published on the National Clinical Programme for Palliative Care website, NCEC web pages and other forums such as the RCPI website;
- Local and national media will be used to publicise both the development process and the availability of the guideline;

- Professional journals and magazines will be used to inform people about guideline development and promote the National Clinical Guideline;
- The communication links developed by healthcare providers, specialist palliative care service providers and specialty societies, service user groups, and universities will be used to promote guideline dissemination and utilisation to all hospitals, hospices, community and homecare services and charitable foundations;
- The educational processes of relevant colleges, professional organisations, healthcare providers and consumer groups, (including conferences, workshops and Continuing Professional Development activities) will be used to promote guideline dissemination and utilisation;
- Potential users and clinical leaders have been involved throughout the guideline development and consultation process, ensuring community ownership of the guideline.

### *1.10.2 Facilitation of action*

It is recognised that there is significant variation in multidisciplinary team structure and responsibilities between care settings. However, the recommendations are deemed relevant for implementation in all healthcare settings. A favourable implementation climate has been created through the work of the National Clinical Programme for Palliative Care to date.

- Stakeholder advisory groups have been established for medical, nursing and allied health professional groups, and members are actively engaged in supporting Clinical Programme activities. Communication pathways exist between the Clinical Programme and the stakeholder advisory groups that will allow for regular communication with staff throughout the process and trouble-shooting of any possible implementation problems.
- A number of implementation tools have been developed and will be made available on the National Clinical Programme for Palliative Care website.
- Audit of important components will be promoted and encouraged, with feedback of the results, to highlight successes as well as challenges in their full implementation.
- Regulators and education providers should give consideration to the education requirements highlighted by the guideline recommendations. Current curricula should be reviewed to incorporate these requirements.
- Development of an app to allow conversion of doses of opioids would support implementation

## 1.11 Further research

The GDG have highlighted a number of areas that they consider of interest when considering future research in the area of cancer pain management:

- An assessment of the patient experience and patient outcomes of using symptom assessment tools.
- An assessment of the patient experience of using symptom assessment tools at different stages of their illness trajectory.
- Development and validation of a proxy assessment tool (or further development of an existing tool for use as a proxy assessment tool) for the assessment of cancer pain.
- An assessment of the effectiveness of a two-step analgesic ladder in the management of cancer pain.
- An assessment of the effectiveness and side effect profile of tapentadol in the management of cancer pain.
- A randomised controlled trial assessing the effectiveness of combination opioid therapy compared with standard opioid therapy in the management of cancer pain.
- Determining the optimal dose of breakthrough short-acting opioid in relation to the patient's regular twenty-four hour opioid requirement.
- Determining the efficacy of topical opioids in the management of painful skin and mucosal lesions.

- Determining the role of genetic polymorphisms in inter-individual variations in response to opioids.
- Determining the efficacy and tolerability of tramadol in a cancer pain setting.
- Determining the efficacy of pregabalin in a cancer pain setting.
- Comparing the efficacy of pregabalin and gabapentin in a cancer pain setting.
- Determining the role of corticosteroids in the management of cancer pain or radiotherapy-induced cancer pain.
- Determining the role for ketamine in a cancer pain setting.
- Determining the role of parenteral lidocaine in the management of opioid refractory cancer pain.
- Determining the role of topical capsaicin in the management of neuropathic pain in a cancer setting.
- Further evaluation of the use of opioids in a renal and liver failure setting.

## 1.12 Resource implications

Estimates indicate that 50%-90% of cancer patients experience pain at some stage (24). The costs of unrelieved pain are potentially very high. Pain is strongly associated with morbid effects on mood and other aspects of quality of life. Substantial costs may result from the management of pain-related complications, such as deep venous thrombosis caused by immobility, or from the need to repeat procedures or tests that could not be performed adequately due to pain (25). Hospitalisations for pain control are common and extremely expensive. For example, an analysis of unscheduled admissions at the City of Hope Medical Center (a comprehensive clinical research, cancer centre and university hospital) estimated an annual cost for uncontrolled cancer pain that exceeded $5 million (26). Attention is drawn to the fact that costs associated with cancer pain can range from costs associated with any or all of the following: analgesics, personnel, surgical and anaesthetic procedures, radiotherapy and other non-drug interventions, reimbursement biases, costs associated with morbidity and legal costs.

In another US-based survey of 373 cancer outpatients, breakthrough cancer pain was shown to predict higher indirect costs (e.g. transport costs, extra household assistance) as well as direct medical costs (27). This has been replicated in the European context where it has also been reported that pain intensity, pain interference and the presence of uncontrolled breakthrough cancer pain predict higher direct and indirect medical expenses within the healthcare system (28). In addition, it has been shown that there is low contribution of opioids to the overall costs in patients with advanced cancer which indicates that this should not be an obstacle to starting this aspect of palliative care earlier in disease progression (29).

Despite recognition of the significant cost burden associated with cancer pain, it remains difficult to quantify the economic impact that can be specifically attributed to the control of pain in cancer. As part of the preparation for this guideline, a formal search for evidence relating to the economic impact of cancer pain and the cost of treatment options was undertaken. There is very little comparative evidence; however, any evidence relevant to this guideline has been included (see Appendix IX).

Thirteen studies of varying methodological rigour and focus were suitable for inclusion in the qualitative synthesis but only one of the studies had been conducted in Ireland. It was the opinion of the guideline group that the literature does not provide sufficient evidence to quantify with a reasonable degree of certainty what impact recommendations will have on resources nationally. Therefore, expert opinion predominantly guides the following assessment of budget impact, and it is emphasised that resource implications associated with implementing this guideline need to be determined at a local level:

Recommendations 1, and recommendations 3-6, aim to consolidate and improve the quality of current clinical practice regarding the assessment and management of cancer pain. The current national standard of practice in this area is unknown, and therefore it is not possible to quantify with a reasonable degree of certainty what impact recommendations will have on resources nationally. The expert opinion of the guideline development group considers it likely that there is a variation in current practice pertaining to these recommendations. While additional training may be required to address practice deficits, continuing professional development activities may be used as a resource neutral method of improving practice. More regular and comprehensive assessment and management of cancer pain may lead to additional time and labour costs for service providers initially but will lead to better and more timely outcomes, and therefore reduce future costs (resulting overall in more efficient use of staff time). The healthcare professionals responsible for these activities are already in post and it is not expected that additional staff would be required to implement these recommendations.

Expert opinion is that the recognition of pain will increase as a result of better assessment practices. As a result, prescription of analgesics may increase. This is likely to vary widely from locality to locality, and local managers should gauge and monitor prescribing trends locally. It is expected that effective management of cancer pain by implementing this guidance may:

- Reduce hospital admissions for crisis interventions or management of adverse effects,
- Reduce the number of contacts with healthcare professionals,
- Reduce the need for further interventions,
- Reduce social care costs associated with unemployment and sickness benefits,

thus offsetting any possible costs arising from any increased analgesic prescribing.

Recommendation 2 focuses on promotion of patient involvement in management of their pain and formalises best practice in this area. Education of service users would be expected to be carried out by relevant healthcare staff involved in the care of the individual (doctor, nurse, allied health professional) and the cost of staff time would be included in their existing contractual payments. The healthcare professionals responsible for these activities are already in post and it is not expected that additional staff would be required to implement these recommendations.

Recommendations 7-39 relate to the use of medications in the management of cancer pain. Guidance is provided on best practice in selection, initiation, titration and discontinuation of medications. Guidance is provided on prevention of adverse effects when using analgesics. Guidance is provided on which analgesics should be used with specialist supervision only and on which analgesics lack evidence of efficacy. As a general principle it is advised that the medication with the lowest cost base where there is no differential benefit between medications is used and a best practice point was added below which applies across the entire guideline and is included in relevant sections. This approach is supported in feedback received from the Medicines Management Programme (see Appendix X).

**Best Practice Point: Pharmacoeconomics**
Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

Training needs in this area are likely to vary between organisations and settings. Although the resource impact is not expected to be significant on a national level, local service providers should investigate the potential resource impact of providing any additional training and/or covering the workload of staff attending training.

The expert opinion of the guideline group is that recommendation 40 represents formalisation of current practice for healthcare professionals, and that therefore implementing these recommendations are unlikely to have a significant cost impact. Organisations are encouraged to evaluate their own practices against the recommendations in the guideline and assess costs locally.

The expert opinion of the guideline group is that recommendation 41 represents formalisation of current practice for healthcare professionals, and that therefore implementing this recommendation is unlikely to have a significant cost impact. A Health Technology Assessment (HTA) of Scheduled Procedures Vertebroplasty and Kyphoplasty for osteoporotic vertebral compression fractures was conducted by HIQA in 2013 (30). Despite the fact that the HTA focused on use of the procedure for osteoporotic vertebral collapse, data on use of the procedure for management of malignant vertebral collapse was also gathered. The HTA noted that that there were approximately 66 vertebroplasties undertaken in 2011 indicating that it is used infrequently. As there is no HIPE code for kyphoplasty, it is coded using the vertebroplasty code (31). HIPE data indicate that 20% of procedures in 2011 related to its use in osteoporosis. 11% of use for lower back pain. 32% of procedures were undertaken in patients with a principal diagnosis of cancer. The data does not provide the number of procedures performed on patients with a secondary diagnosis of malignancy with spinal involvement (32). HIPE data indicates that vertebroplasties were carried out in each of the hospital groups, with the exception of the MidWest, in 2011.

The estimated average cost of a vertebroplasty in Ireland in 2011 calculated in the HTA is included in Table 1. The HSE National Casemix Programme does not include a diagnosis related group (DRG) specific to vertebroplasty. Therefore, more general DRG codes for musculoskeletal procedures are included to give an estimate of the cost. HIPE discharge data suggests that 60% (128A 30%, 128B 30%) of vertobroplasty procedures in 2011 used these codes. This code equates to an approximate total cost of €420,000 based on 66 procedures or a weighted average cost of €6,636 per procedure (30). These estimated procedure costs likely underestimate the actual cost of vertebroplasty given the acquisition cost of the cement kit alone in the UK was estimated to range from £800 (lower viscosity cement) to £1,403 (high viscosity cement, average of three prices: £1,546, £1,472 and £1,193 used by the assessment group for NICE, Johnson and Johnson and Medtronic cost effectiveness models respectively) in 2009(33, 34). Also, the average acquisition cost of the kyphoplasty kit was estimated as £2,492 (£2,639, £2,842 and £1,996: NICE, Johnson and Johnson and Medtronic respectively)(33, 34).

Chew et al. 2013 carried out a study to ascertain prospectively the health service cost of vertebroplasty in a cohort of consecutive patients with spinal metastases treated in Glasgow, Scotland (35). Percutaneous vertebroplasty was performed under conscious sedation and local anaesthetic in the Interventional Suite with fluoroscopic guidance. Data were collected prospectively on standard forms. Quality of life questionnaires (EQ-5D) were filled out pre-, 6 weeks, and at 6 months post-vertebroplasty. The majority of the procedures were performed on an outpatient basis (8/11). The median duration of the procedure was 60 min (range 40-80 min) with a further 60 min spent in the recovery room (range 10-230 min). Personnel involved included a consultant radiologist, a radiology registrar, four nurses, and two radiographers. The average cost of vertebroplasty per patient, including consumables, capital equipment, hotel/clinic costs, and staffing, was £2213.25 (95% CI £729.95). The mean EQ-5D utility scores increased from 0.421 pre-treatment to 0.5979 post-treatment (p=0.047). The visual analogue scale (VAS) of perceived health improved from a mean of 41.88 to 63.75 (p=0.00537). The authors concluded that health service costs for percutaneous vertebroplasty in patients with spinal metastases is significantly lower than previously estimated and is in keeping with that of other palliative radiological procedures (35).

The expert opinion of the GDG is that recommendation 42 represents formalisation of current practice for healthcare professionals, and that therefore implementing this recommendation

is unlikely to have a significant cost impact. It is possible that formalising the recommendation could lead to an increase in the overall number of referrals for these procedures. However, the recommendation relates to those patients whose pain has proved difficult to control with other methods and therefore other treatment modalities have been explored before consideration of this procedure.

**Table 1** Estimated cost of percutaneous cementoplasty in Ireland (based on 2011 costs and activity)

(Source: Health Information and Quality Authority. Health Technology Assessment of Scheduled Procedures Vertebroplasty and kyphoplasty for osteoporotic vertebral compression fractures. Dublin: Health Information and Quality Authority; 2013.)

| DRG Code | Description | Cost/case (€) |
|---|---|---|
| 128A | Other musculosketal procedures with catastrophic complications | 14,134 |
| 128B | Other musculosketal procedures without catastrophic complications | 4,669 |
| 128 | Other musculosketal procedures | 1,799 |
| - | Outpatient Appointment | 130 |

*Data Summary from the HSE National Casemix programme based on activity and costs reported by 39 participating hospitals. (Note there is no specific code for vertebroplasty, the nearest codes are included and as such provide an estimate of the cost.)*

## 1.13 Procedure for update of the National Clinical Guideline

This guideline was published in November 2015 and will be reviewed in 3 years by the NCPPC. This will consist of formal evidence searches on the clinical questions and recommendations that follow a standardised methodology (36). Surveillance of the literature base will be carried out periodically by the NCPPC so that the guideline will maintain its relevance and currency. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCPPC and NCEC websites.

## 1.14 Audit and monitoring

To ensure that this guideline positively impacts on patient care, it is important that implementation is audited. Audit is recommended to support continuous quality improvement in relation to the implementation of the National Clinical Guideline.

Quality assurance and quality improvement activities have a complementary relationship with clinical guidelines. Quality assurance activities encourage the implementation of guidelines, and guidelines are a crucial component of quality assurance activities. A number of Excel based resources have been developed to assist in audit activities:

- Baseline assessment tool
- Audit tool
- Action plan template

These tools may be found on the National Clinical Programme for Palliative Care website.

**Table 2** Suggested recommendations for audit

| Recommendations for Audit | Recommendation |
|---|---|
| **Principles of Pain Management** | |
| Cancer pain management plans should address the physical, psychosocial, emotional and spiritual domains of patient care. Addressing the physical aspects of cancer pain alone is insufficient. | **1** |
| Patients should be given appropriate information about their pain, and pain management, and be encouraged to participate in their treatment plan. | **2** |
| Systematic assessment of cancer pain including physical, psychological, and spiritual domains is essential.<br>The patient should be the prime assessor of his or her pain. | **3** |
| Cancer patients should have their pain managed in accordance with the WHO Cancer Pain Relief guidance. | **6** |
| **Opioids: Weak opioids** | |
| Weak opioids may be used in the treatment of mild to moderate pain. They may be used in conjunction with a non-opioid analgesic. Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. | **7** |
| **Opioids: Choice of Opioid** | |
| Oral morphine sulphate, hydromorphone and oxycodone may be used as first line treatment in the management of moderate to severe cancer pain. Consider using opioids with the lowest acquisition cost when all other considerations are equal. | **8.1** |
| **Opioids: Route of Administration** | |
| The oral route should be used for administration of opioids, if practical and feasible. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes. | **9** |
| Use of the transdermal route is suitable for patients who have stable pain. Patients should be titrated to adequate pain relief with oral or parenteral opioid pain medications prior to the initiation of transdermal patches. Medication for breakthrough pain should also be prescribed. | **14** |
| **Opioids: Dosing Regimen** | |
| When starting treatment with strong opioids, offer patients with advanced and progressive disease regular oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain. | **9, 10, 11** |
| **Opioid Side-effects** | |
| It is important to anticipate and monitor patients for opioid side-effects and manage these at the earliest opportunity to prevent unnecessary morbidity. | **17.1** |
| Opioid rotation should be performed where pain is poorly controlled, or side-effects are intolerable. | **20** |
| Evidence-based dose conversion ratios should be applied, taking into account individual patient factors. Pain control should be assessed regularly and doses titrated as required. | **21** |

| Recommendations for Audit | Recommendation |
|---|---|
| **Non-Opioid Pharmacological Management;Adjuvant analgesics** | |
| In patients with cancer-related neuropathic pain, anti-epileptic and antidepressant medications should be considered, with careful monitoring of side effects. | **32** |
| Bisphosphonates should be considered as part of a therapeutic regime for the treatment of cancer pain associated with bone metastases; however, there is insufficient evidence to recommend them as first line therapy. | **33** |
| **Specialist input** | |
| Methadone may be used for the treatment of moderate or severe cancer pain.<br><br>Methadone use is only advised through the guidance of specialist palliative care professionals. | **8.3**<br><br>**8.4** |
| Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made. Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. | **15** |
| **Renal impairment** | |
| In renal impairment, all opioids should be used with caution, and with consideration of reduced doses and/or frequency of administration. Specialist advice should be sought in moderate to severe renal impairment.<br><br>The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain, when needed.<br><br>Close monitoring of pain and for signs of opioid toxicity is required.<br><br>Alfentanil and fentanyl are the safest opioids of choice in patients with stages 4 or 5 kidney disease (estimated glomerular filtration rate <30 ml/ min/1.73 $m^2$).<br><br>Paracetamol is considered the non-opioid analgesic of choice for mild-to-moderate pain in chronic kidney disease patients.<br><br>Adjuvant analgesics may require dose adjustment in patients with renal impairment. | **38** |
| **Hepatic Impairment** | |
| In advanced liver disease:<br>Opioids should be used with caution in patients with advanced liver disease. Dosage recommendation should be patient specific and specialist advice sought.<br><br>The transdermal route should be avoided, as drug absorption can be variable and unpredictable.<br><br>Sustained release preparation should be avoided. | **39** |

## 1.15 Glossary of terms, definitions and abbreviations

The main referenced definitions are in the relevant sections as they arise. A glossary of abbreviations is available in Appendix XI.

## 1.16 Further resources and accompanying documents

The following documents and resources are available at http://health.gov.ie/patient-safety/ncec/national-clinical-guidelines-2 and/or http://www.hse.ie/palliativecareprogramme

- Pharmacological Management of Cancer Pain in Adults Executive Summary, National Clinical Guideline No. 9
- Pharmacological Management of Cancer Pain in Adults Quick Reference Guide: Opioids and non-opioids
- Pharmacological Management of Cancer Pain in Adults Quick Reference Guide for Renal and Hepatic Impairment
- Pharmacological Management of Cancer Pain in Adults Audit Tool
- Pharmacological Management of Cancer Pain in Adults Audit Tool Guidance
- Pharmacological Management of Cancer Pain in Adults Action Plan Template
- *Relief from Cancer Pain*, Patient information booklet
- Management of Constipation in Adult Patients Receiving Palliative Care, National Clinical Guideline No. 10
- Palliative Care Needs Assessment Guidance
- Palliative Care Competence Framework
- Glossary of Terms

# 2 National Clinical Guideline recommendations

## 2.1 Summary National Clinical Guideline recommendations

Key recommendations are outlined in green font and are numbered **R1-R42**; with the strength of evidence for the recommendation to follow (A/B/C/D), based on the CEBM method of Oxford University(1). Grade A recommendations represent the strongest level of recommendation based on the strongest evidence, and Grade D recommendations are based on lower levels of evidence.

This guideline applies to healthcare professionals involved in the management of cancer pain. This includes Palliative Care staff, Physicians, Surgeons, General Practitioners, Pharmacists and Nursing staff in hospital, hospice and community-based settings. The guideline recommendations indicate where specialist advice should be sought.

## Principles of pain management

Cancer pain impacts on a patient's physical, psychosocial and emotional wellbeing.

### R 1 Domains of cancer pain

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | Cancer pain management should address the physical, psychosocial and emotional domains of patient care. Addressing the physical aspects of cancer pain alone is insufficient. |

Involving and educating patients about their pain management improves patient understanding and can decrease pain intensity.

### R 2 Patient involvement in cancer pain management

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | Patients should be given appropriate information about their pain, and pain management, and be encouraged to participate in their treatment plan. |

The cornerstone of comprehensive pain assessment is the taking of a detailed patient history and the performance of a thorough physical examination. The psychological and spiritual impact of a patient's pain should be considered. Pain is a subjective experience.

### R 3 Assessment of cancer pain

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **C** | Systematic assessment of cancer pain including physical, psychological, and spiritual domains is essential.<br><br>The patient should be the prime assessor of his or her pain. |

A number of assessment tools exist in relation to the physical, psychosocial and spiritual domains of cancer pain.

### R 4 Assessment tools

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | The use of pain and other symptom assessment tools should be considered as part of the comprehensive ongoing evaluation of cancer patients. |

In patients with cognitive impairment, a systematic approach to pain assessment including the use of pain assessment tools, behavioural observations, surrogate reporting and analgesic trials is recommended.

### R 5 Pain assessment in patients with cognitive impairment

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | Pain assessment in the cognitively impaired should involve self-reported pain scales where appropriate. Observational pain rating scales and behavioural assessment tools should be considered for those who cannot complete a self-assessment scale. |

The WHO analgesic ladder from WHO Cancer Pain Relief guidance has been extensively validated and shown to be effective in the management of pain in the majority of cancer patients.

### R 6 The World Health Organisation (WHO) Cancer Pain Relief Guidance

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **C** | Cancer patients should have their pain managed in accordance with the World Health Organisation (WHO) Cancer Pain Relief guidance. |

**How to use the WHO analgesic ladder** (see Table 4 in Section 2.2.10.1 and reproduced here) (adapted from SIGN Guidelines (2))

| WHO analgesic ladder | Score on numerical rating scale | Analgesic of choice |
|---|---|---|
| Step 1:<br>mild pain | 1 to 2<br>out of 10 | Non-opioid (Paracetamol/NSAID)<br>+/- Adjuvant |
| Step 2:<br>mild to moderate pain | 3 to 6<br>out of 10 | Weak opioid (Codeine/ Tramadol*)<br>+/- Non-opioid<br>+/- Adjuvant |
| Step 3:<br>severe pain | 7 to 10<br>out of 10 | Strong opioid (Morphine sulphate/ Oxycodone/ Hydromorphone/ Fentanyl)<br>+/-Non-opioid<br>+/- Adjuvant |

* Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. See recommendation 7.

It is imperative that the clinician selects the strength of opioid analgesic according to the current severity of pain (i.e. the clinician can start at step 3 if the patient has severe pain).

## Opioids

### *Choice of opioid*

**Opioids for mild to moderate pain**

Codeine, dihydrocodeine and tramadol are examples of weak opioids that are commonly prescribed for use at step two of the WHO ladder. There is an evidence base to support the use of codeine and codeine/paracetamol in cancer pain. There is insufficient evidence to support the use of oral tramadol or tapentadol in preference to codeine/paracetamol for mild to moderate cancer pain.

**R 7 Weak opioids**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| C | Weak opioids may be used in the treatment of mild to moderate pain. They may be used in conjunction with a non-opioid analgesic. Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. |

**Opioids for moderate to severe pain**
The available evidence demonstrates that the efficacy and tolerability of morphine sulphate, oxycodone, hydromorphone and methadone are equivalent, and these agents are all valid choices as first and subsequent choice opioids for moderate to severe cancer pain.

Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients; they may be associated with less constipation and good patient compliance, but their pharmacokinetic and dynamic characteristics present challenges.

**R 8 Choice of opioid**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | **8.1** Oral morphine sulphate, hydromorphone and oxycodone may be used as first line treatment in the management of moderate to severe cancer pain. |
| **B** | **8.2** Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients. |
| **D** | **8.3** Methadone may be used for the treatment of moderate or severe cancer pain. |
| **D** | **8.4** Methadone use is only advised through the guidance of specialist palliative care professionals. |

**Route of Administration of opioid**
The oral route should be used for administration of opioids, if practical and feasible. Alternative routes are found to be as effective from an efficacy and side effect profile perspective.

**R 9 Route of administration of opioid**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | The oral route should be used for administration of opioids, if practical and feasible. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes. |

## Oral administration of opioids
Morphine sulphate, oxycodone and hydromorphone can be administered as immediate (IR) or modified release (MR) (sometimes called 'sustained release' or SR). Peak plasma concentrations normally occur within one hour of administration of an immediate release morphine sulphate preparation, with reasonably rapid onset of analgesia, which then lasts for about 4 hours. In contrast, modified release formulations produce a delayed peak plasma concentration after 2-6 hours, and analgesia lasts for 12 to 24 hours.

In terms of analgesic efficacy, there is no difference between four-hourly, twelve-hourly and twenty-four-hourly dosing of morphine sulphate, oxycodone or hydromorphone preparations, once they are correctly administered.

### R 10 Oral opioid dosing schedule

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | As there is no difference between the available oral opioid preparations in terms of analgesic efficacy, oral opioid scheduling should be based on patient preference and ease of compliance. |

Opioid treatment can be adequately and safely started with a number of therapeutic approaches.

### R 11 Oral opioid treatment

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **C** | Oral opioid titration can be adequately and safely commenced and titrated using either oral immediate release preparations, or modified release preparations. |

See Table 6 and Table 7 in Section 2.3.2.1 and reproduced here.

**Table 6** Titration using immediate release oral preparations

**Titration Using Immediate Release Oral Preparations**
(Using oral morphine sulphate as an example)

- Use immediate release morphine sulphate, given every 4 hours, and the same dose for breakthrough pain. This rescue dose may be given as often as required and the total daily dose of the morphine sulphate should be reviewed daily.
- If pain returns consistently before the next regular dose is due, the regular dose should be increased. Patients stabilised on regular oral morphine sulphate require continued access to a rescue dose to treat breakthrough pain.
- When a patient's pain has been controlled with immediate release morphine sulphate, the 24 hour dose can be converted into modified 12 hour release preparation.

For example*
- A patient is taking immediate release morphine sulphate 10mg every four hours.
- This means that they are taking 60mg of morphine sulphate in 24 hours.
- The patient can be commenced on morphine sulphate 30mg twice daily, if using a 12 hourly preparation

**Table 7** Titration using modified release oral preparations

**Titration Using Modified Release Oral Preparations**
(using oral morphine sulphate as an example)

- Use a modified release preparation, such as a 12 hourly morphine sulphate preparation (e.g. MST®) prescribed twice daily. Co-prescribe an immediate release oral morphine sulphate preparation, to be taken as often as required as a breakthrough dose. See section 2.3.2.2 on appropriate dosage for breakthrough pain prescribing.
- After 24 hours, assess the effectiveness of the regimen based on clinical assessment of the patient and calculation of the number of breakthrough analgesic doses required. Titrate the modified release formulation accordingly

For example*
- A patient is taking modified release oral morphine sulphate 15mg bd (e.g. MST® 15mg bd) and has required 4 breakthrough doses of immediate release oral morphine sulphate 5mg
- This means the patient has taken 50mg of morphine sulphate in 24 hours
- The patient's modified release oral morphine sulphate should be titrated to 25mg twice daily (also adjust breakthrough dose)
- A further assessment of pain and potential dose titration is made after a further 24 hours, and so forth.

**** This conversion is by way of example. Individualised titration is always recommended and is dependent on clinical assessment.***

## Breakthrough pain

Breakthrough pain is a transitory exacerbation of pain experienced by the patient with stable and adequately controlled baseline (background) pain. The use of a pharmacological 'rescue' or 'breakthrough' dose of analgesia is widely accepted as the management of breakthrough pain.

Breakthrough pain is common and can have a negative impact on quality of life.

Patients should have breakthrough medication prescribed and this dose should be titrated according to the individual, and to the type of breakthrough pain being experienced.

### R 12 Breakthrough pain

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations.<br><br>More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed.<br><br>As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is recommended. |

**Best Practice Point**
The dose of breakthrough opioid can be calculated as either:

1/6 of the total 24hr dose (most commonly used calculation)

or,

10%-20% of the total 24hr dose

EXCEPT where fast acting fentanyl preparation are being prescribed. Here, the rescue (breakthrough) dose is independent of the background opioid analgesic dose. Start at lowest available strength, and titrate according to manufacturer's guidance.

### Alternative routes of administration of opioids

#### Parenteral opioids

Subcutaneous and intravenous routes of administration are feasible, effective and safe for the administration of opioid medication in cancer pain.

Indications for the use of continuous infusion include:

- Intractable vomiting
- Severe dysphagia
- Patient too weak to swallow oral medication
- Decreased level of consciousness
- Poor gastrointestinal absorption
- Poor patient compliance.

#### R13 Parenteral routes of opioid administration

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | **13.1** Subcutaneous and intravenous routes may be used where the oral route is not feasible. |
| **C** | **13.2** The average relative potency ratio of oral morphine sulphate to subcutaneous or intravenous morphine sulphate is between 2:1 and 3:1, with variability between patients. |

#### Transdermal opioids

Transdermal fentanyl and buprenorphine patches are valid alternative delivery systems for patients with stable pain who require regular opioid analgesia.

#### R 14 Transdermal opioids

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | Use of the transdermal route is suitable for patients who have **stable** pain. Patients should be titrated to adequate pain relief with oral or parenteral opioid pain medications prior to the initiation of transdermal patches. Medication for breakthrough pain should also be prescribed. |

**Transmucosal opioids**
Opioid administration via the buccal, sublingual or nasal mucosa is indicated only for the treatment of breakthrough pain. Any role in the treatment of continuous pain is limited.

**Spinal opioids**
Spinal opioid therapy may be effective for treating cancer pain where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia.

**R15 Spinal opioids**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. The responsible physician caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made.<br><br>Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. |

**Topical opioids**
There is limited evidence to support the use of topical opioids in the management of painful malignant skin and mucosal lesions.

**R16 Topical opioids**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | Whilst there is support for the use of topical opioids, there is insufficient evidence to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, method of titration, carrier agent or most suitable wounds for this treatment. |

## Opioid side-effects

### R 17 Opioid side-effects

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | **17.1** It is important to anticipate and monitor patients for opioid side-effects and manage these at the earliest opportunity to prevent unnecessary morbidity. |
| **D** | **17.2** The current evidence is too limited to provide evidence-based recommendations for the use of anti-emetics in opioid-induced nausea/vomiting in cancer patients. Choice is therefore based on knowledge of aetiology and expert opinion. |
| **D** | **17.3** In the management of opioid-induced constipation, the combination of a softener and stimulant laxative is generally recommended, and the choice of laxatives should be made on an individual basis[1]. |
| **D** | **17.4** The use of peripheral opioid receptor antagonists (methylnaltrexone) should be restricted to those patients whose treatment is resistant to traditional laxatives. |

Opioids may cause neuropsychological side-effects, such as sedation, cognitive dysfunction, sleep disturbance, myoclonus, hyperalgesia and delirium. Delirium is a frequent and often multi-factorial complication in advanced cancer. Delirium precipitated by opioids is frequently reversible.

### R18 Neuropsychological opioid side-effects

| | |
|---|---|
| **B** | **18.1** Opioid reduction or rotation should be considered as a useful strategy to manage opioid side-effects. |
| **D** | **18.2** Given the present available knowledge, no recommendation can be made for or against the use of specific drugs for the relief of opioid-induced myoclonus, sleep disturbance or hyperalgesia. |
| **B** | **18.3** The treatment of delirium firstly involves the search for an identifiable underlying cause and the treatment of this cause. |
| **D** | **18.4** Haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances. Opioid reduction or rotation should be considered. |

## Opioid toxicity

There is a wide variation in the dose of opioid that is toxic, both between individuals and over time. Patients may develop toxicity on titration of opioids; however, toxicity also may occur in patients who have been relatively stable on long-term opioid therapy.

Toxicity can be a frightening and even life threatening experience, but is usually reversible.

1 See NCEC National Clinical Guideline 10. Management of Constipation in Adults Patients Receiving Palliative Care (Nov 2015)

Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery of the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression.

### R 19 Opioid toxicity

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | If toxicity is experienced on a stable dose of an opioid which has been previously tolerated, other factors should be sought and treated such as infection, dehydration, renal impairment or hypercalcaemia. |

**Best Practice Point: Management of opioid toxicity**

Renal and hepatic function should be checked and other causes of systemic deterioration excluded e.g. infection, hypercalcaemia. Any reversible precipitating cause should be treated.

Mild opioid toxicity**:** In mild opioid toxicity; reduce the dose of opioid. Ensure adequate hydration and treat any underlying cause. If agitation/confusion are problematic, consider a neuroleptic such as haloperidol.

Moderate opioid toxicity**:** If respiratory rate ≥ 8/min, oxygen saturations are normal and the patient is not cyanosed and is easily rousable, omit the next dose (or stop infusion/remove patch) of regular opioid immediately, and adopt a 'wait and see' approach. When the situation is more stable, either omit or reduce further doses and re-assess pain before re-introducing regular opioid therapy.

Severe opioid toxicity**:** If respiratory rate is 8/min or less, oxygen saturations are abnormal or the patient is cyanosed, urgent admission is indicated. Consider reversal of respiratory depression using naloxone; use reversing agents cautiously. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. The patient's background analgesia will subsequently need to be reviewed. Seek specialist palliative medical advice for continuing problems, particularly if transdermal patches have been used.

**Use of naloxone for reversal of opioid side-effects**

(Palliative Adult Network Guidelines 2011 (19), based on the recommendations of the American Pain Society)

If the patient's respiratory rate is< 8/min, the patient is barely rousable/unconscious and/or is cyanosed:

- Dilute a standard ampoule containing naloxone 400 micrograms to 10ml with sodium chloride 0.9% for injection.
- Administer 0.5ml (20micrograms) IV every 2 minutes, until the patient's respiratory status is satisfactory
- Further boluses may be necessary because naloxone is shorter-acting than morphine sulphate and other opioids

Close observation is needed to ensure that the patient is breathing satisfactorily and that pain control is maintained.

If using naloxone, seek specialist advice for management of opioid side-effects and for ongoing cancer pain management.

**Opioid rotation**
Opioid rotation is the term given to the clinical practice of substituting one opioid – the 'initial opioid' - with another, in order to obtain a satisfactory balance between pain relief and side-effects.

Opioid rotation utilises inter-individual variability and the phenomenon of incomplete cross-tolerance in order to maximise the analgesic effect of a new opioid while minimising side effects.

**R 20 Opioid rotation**
*CEO/General/Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | Opioid rotation should be performed where pain is poorly controlled, or side-effects are intolerable. Opioid rotation should only be performed by those with relevant clinical expertise. |

**Opioid potency ratios**
When converting from one strong opioid to another, the initial dose of the new opioid should depend on the relative potency of the two drugs, as well as other clinical factors. (See Table 11 *NCEC National Clinical Guideline Pharmacological Management of Cancer Pain in Adults*)

**R 21 Evidence for relative opioid potencies**
*CEO/General/Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **D** | Evidence-based relative potency ratios should be applied, taking into account individual patient factors. Pain control should be assessed regularly and doses titrated as required. |

**Processes in converting opioid doses** (See Table 11 in Section 2.3.5.1 and reproduced here)

| Converting From | Converting To | Process |
|---|---|---|
| **Oral (mg)** | **Oral (mg)** | |
| Codeine | Morphine sulphate | • Divide by 10 |
| Tramadol | Morphine sulphate | • Divide by 5 – 10 |
| Morphine sulphate | Oxycodone | • Divide by 1.5 -2 |
| Morphine sulphate | Hydromorphone | • Divide by 5 |
| **Oral (mg) / 24 hours** | **Subcutaneous / 24 hours** | |
| Morphine sulphate | Fentanyl (mcg) | • Divide by 100 to obtain equivalent fentanyl dose in mg.<br>• Multiply by 1000 to obtain dose in mcg / 24 hrs. |
| Morphine sulphate | Alfentanil (mg) | • Divide by 32 |
| **Oral (mg) / 24h hours** | **Transdermal (mcg / hour)** | |
| Morphine sulphate | Buprenorphine | • Divide by 75 to obtain equivalent buprenorphine dose in mg.<br>• Multiply by 1000 to obtain dose in mcg / 24 hrs.<br>• Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength. |
| Morphine sulphate | Fentanyl | • Divide by 100 to obtain equivalent fentanyl dose in mg.<br>• Multiply by 1000 to obtain dose in mcg / 24hrs.<br>• Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength. |
| | Alternatively, use Table 9 in the NCEC National Clinical Guideline, *Pharmacological Management of Cancer Pain in Adults* to obtain closest appropriate patch strength | |

**R 22-26 please refer to Opioid Equivalence Summary Table (Table 12) below for guidance on practical conversions**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | A relative potency ratio of oral morphine sulphate to oral oxycodone of between 1.5 : 1 and 2 : 1 is recommended. |
| **C** | A relative potency ratio of oral morphine sulphate to oral hydromorphone of 5 : 1 is recommended. |
| **C** | A relative potency ratio of oral morphine sulphate to transdermal buprenorphine of 75 : 1 is recommended. |
| **B** | A relative potency ratio of oral morphine sulphate to transdermal fentanyl of 100 : 1 is recommended. |
| **D** | Methadone is a complex strong analgesic agent and should be used under specialist supervision only. |

**Practical Guidance**

1. Most relative potencies relate to the relative potency of a strong opioid in relation to morphine sulphate. When switching from a strong opioid other than morphine sulphate, it may be necessary to convert the dose of the initial opioid to the oral morphine sulphate equivalent dose, and then use this to determine the dose of the new opioid.
2. Buprenorphine is a partial mu-receptor agonist and a partial kappa-receptor antagonist and has slow receptor dissociation that may impede the full effectiveness of other opioids used.
3. Fentanyl and buprenorphine are most commonly used via a transdermal patch and in patients with stable pain where the oral route is not possible or not convenient. When using patches, it is recommended that an interval of at least three days should be used between dose changes. This is to allow time for steady state of the drug to be achieved. When converting from a patch to an oral or parenteral opioid, this also needs to be considered: please see full guideline for further guidance, or seek specialist advice.

**Opioid Equivalence Summary Table**

Guidelines for use:

- relative potency ratios should only be used as an approximate guide and individual and clinical factors should be taken into account
- on opioid rotation, particularly at high doses, a dose reduction of 25 – 50% should be considered to account for incomplete cross-tolerance
- pain control should be assessed regularly, and doses titrated as required.

**Opioid equivalence summary table** (See Table 12 in Section 2.3.5.1 and reproduced here)
(all recommendations Grade C)

| Morphine | | Codeine | Tramadol | Oxycodone | | Hydromorphone | | Buprenorphine | | Fentanyl | Morphine | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *(mg / 24 hrs)* | | *(mg / 24 hrs)* | *(mg / 24 hrs)* | *(mg / 24 hrs)* | | *(mg / 24 hrs)* | | *(mcg / hour) Butrans®* | *(mcg / hour) Transtec®* | *(mcg / hour)* | *(mg / 24 hrs)* | |
| **Oral** | **S/C** | **Oral** | **Oral** | **Oral** | **S/C** | **Oral** | **S/C** | **Transdermal** | | **Transdermal** | **Oral** | **S/C** |
| 5 | 2.5 | 60 | 50 | - | - | - | - | - | | - | 5 | 2.5 |
| 10 | 5 | 120 | 100 | - | - | - | - | 5 | See Butrans® | | 10 | 5 |
| 20 | 10 | 240 | 200 | - | - | 4 | 2 | 10 | | 12 | 20 | 10 |
| 30 | 15 | Titrate to strong opioid | | 20 | 10 | 6 | 3 | | | | 30 | 15 |
| 40 | 20 | | 400 | | | 8 | 4 | 20 | | 18 | 40 | 20 |
| 50 | 25 | | | - | - | 10 | 5 | | | | 50 | 25 |
| 60 | 30 | | | 40 | 20 | 12 | 6 | See Transtec® | 35 | 25 | 60 | 30 |
| 70 | 35 | | | | | 14 | 7 | | | | 70 | 35 |
| 80 | 40 | | | | | 16 | 8 | | | 37 | 80 | 40 |
| 90 | 45 | | Titrate to strong opioid | 60 | 30 | 18 | 9 | | 52.5 | | 90 | 45 |
| 100 | 50 | | | | | 20 | 10 | | | | 100 | 50 |
| 110 | 55 | | | | | - | - | | | 50 | 110 | 55 |
| 120 | 60 | | | | | 24 | 12 | | | | 120 | 60 |
| 130 | 65 | | | 80 | 40 | - | - | | 70 | | 130 | 65 |
| 140 | 70 | | | | | 28 | 14 | | | 62 | 140 | 70 |
| 150 | 75 | | | | | - | - | | | | 150 | 75 |
| 160 | 80 | | | 100 | 50 | 32 | 16 | | | | 160 | 80 |
| 170 | 85 | | | | | - | - | Consider the use of an alternative opioid | | 75 | 170 | 85 |
| 180 | 90 | | | | | 36 | 18 | | | | 180 | 90 |
| 190 | 95 | | | | | - | - | | | | 190 | 95 |
| 200 | 100 | | | | | - | - | | | - | 200 | 100 |

| Converting From | Converting To | Process |
|---|---|---|
| **Oral** | **Oral** | |
| Codeine | Morphine sulphate | Divide by 10 |
| Tramadol | Morphine sulphate | Divide by 5 – 10 |
| Morphine sulphate | Oxycodone | Divide by 1.5 – 2 |
| Morphine sulphate | Hydromorphone | Divide by 5 |
| **Converting From** | **Converting To** | **Process** |
| **Oral (mg / 24 hrs)** | **S/C (mg / 24 hrs)** | |
| Morphine sulphate | Alfentanil | Divide by 32 |

### Managing cancer pain in patients with a history of addiction

See Section 2.3.5 of *National Clinical Guideline Pharmacological Management of Cancer Pain in Adults* which contains recommendations 26-29.

Addiction is a syndrome and pattern of substance misuse, with biological, psychological and social aspects. A history of addiction to opioids, such as heroin, may compromise the effective control of cancer pain. In addition, patients may be receiving treatment for an addiction, such as methadone maintenance therapy (MMT), which may further complicate management.

Patients with a history of addiction may have co-morbidities such as depression and anxiety, further complicating management of their physical pain. Social aspects influencing care include a complex social milieu, social exclusion and reduced opportunities. Communication with the patient's addiction services and primary care team should be maintained.

Specialist advice should be sought. A multidisciplinary approach that involves Addiction Services should be adopted.

## Non-opioid pharmacological management

### Paracetamol

Paracetamol is well established as an effective and well tolerated agent in the management of mild to moderate pain. Paracetamol continues to have a role as an analgesic in patients with cancer pain, in accordance with the WHO Cancer Pain Relief guidance.

**R 30 Paracetamol**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | **30.1** Paracetamol should be considered for patients with mild to moderate cancer pain, in accordance with the WHO Cancer Pain Relief guidance. |
| **A** | **30.2** There is insufficient evidence to support the addition of paracetamol for analgesic purposes in patients taking high doses of step 3 opioid medication in a cancer setting. |

### Non steroidal anti-inflammatory drugs (NSAIDS)

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted as a treatment option for cancer pain. The WHO guidelines suggest an NSAID as a potential non-opioid for use at the first step of the WHO analgesic ladder, and throughout a patient's escalating pain trajectory.

Whilst NSAIDs are effective for the treatment of cancer pain, there is no clear evidence to support the superior safety or efficacy of one particular NSAID over another. In terms of choice of NSAID, there appears to be reduced cardiovascular risk for low dose ibuprofen (up to 1200mg/day), or for naproxen.

### R 31 NSAIDs

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | **31.1** NSAIDs should be considered for the treatment of cancer pain, both as single agents and in combination with step 3 opioids. |
| **D** | **31.2** Risk stratification and identification of the individual cardiovascular and gastrointestinal risk factors should inform the decision regarding choice of NSAID, and gastroprotective strategy. |
| **C** | **31.3** Patients taking NSAIDs who are at high risk of gastrointestinal complications should be prescribed either double dose H2-antagonists or a proton pump inhibitor as pharmacological prophylaxis. Patients in this category could also be considered for a COX-2 inhibitor, depending on their cardiovascular risk factor profile. |

## Anti-depressants and anti-epileptics

Neuropathic pain mechanisms are present in up to 40% of patients with cancer pain. In order to achieve optimum pain control in these patients, it is often necessary to combine adjuvant analgesics, such as antidepressants and/or anti-epileptics, with standard opioid therapy.

There is evidence that antidepressants and anti-epileptics may improve cancer-related neuropathic pain. There is evidence in the non-cancer setting to support the use of antidepressants, including tricyclic antidepressants, venlafaxine and duloxetine, which may be extrapolated to the treatment of cancer related neuropathic pain. There is insufficient evidence to support a recommendation on the use of selective serotonin reuptake inhibitors (SSRIs). There is evidence in the cancer setting to support the use of gabapentin. There is evidence from the non-cancer setting to support the use of pregabalin, at suitable doses for the treatment of neuropathic pain.

### R 32 Antidepressants and anti-epileptics

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | In patients with cancer-related neuropathic pain, anti-epileptic and antidepressant medications should be considered, with careful monitoring of side effects. |

## Other adjunct agents

### R 33 – 37

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation*

| | |
|---|---|
| **A** | **33.** Bisphosphonates should be considered as part of a therapeutic regime for the treatment of cancer pain associated with bone metastases; however, there is insufficient evidence to recommend them as first line therapy. |
| | **34.** Corticosteroids may have a limited role in the management of cancer-related pain, however there is insufficient evidence to allow a recommendation. |

| | |
|---|---|
| **D** | **35.** There is insufficient evidence to permit a recommendation to be made regarding the use of ketamine for the management of cancer pain. |

| | |
|---|---|
| **D** | **36.1** Intravenous lidocaine may be a useful adjunct in the treatment of opioid-refractory cancer pain. Specialist advice should be sought if intravenous lidocaine is being considered. |
| **D** | **36.2** There is limited evidence to support the use of topical lidocaine plaster in cancer pain. |

| | |
|---|---|
| | **37.** There is insufficient evidence to recommend the use of topical capsaicin for the treatment of cancer pain. It may provide some degree of relief in non-cancer related neuropathic pain conditions and could therefore be considered a worthwhile option as an adjunctive treatment. |

The anti-inflammatory effects of corticosteroids have been reported to be useful in the management of cancer-related neuropathic and bone pain. Despite vast experience with corticosteroid use, there is a lack of robust evidence to support their role as an analgesic agent. Topical creams containing capsaicin are used to treat a variety of conditions, including neuropathic pain.

## The use of opioids and other analgesics in patients with renal impairment

- Renal impairment is common in the setting of advanced cancer, and alters the pharmacokinetics of opioids and their metabolites, thus increasing the potential for opioid toxicity.
- The presence of renal impairment is not a reason to delay or avoid using opioid analgesia in patients with cancer related pain.
- Consideration should be given to
  - Choice of opioid based on pharmacokinetic profile
  - Use of immediate release formulations over long acting formulations
  - Dose reduction
  - Increase in dosing interval
  - Frequent clinical review.
- The quality of clinical evidence regarding the choice of opioids in renal impairment is low. Therefore, the choice of opioid in renal impairment should be based on the metabolite profile of individual opioids (see Risk stratification of individual opioids table below)
- Paracetamol is the non-opioid analgesic of choice in the setting of renal impairment. Other non-opioid analgesics may require dose adjustment, in particular in the dialysis setting, and specialist advice e.g. Renal Drug Handbook, should be sought.

### R 38 Opioids in renal impairment

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| C | In renal impairment, all opioids should be used with caution, and with consideration of reduced doses and/or frequency of administration.<br><br>Specialist advice should be sought when prescribing opioids in moderate to severe renal impairment.<br><br>The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain, when needed.<br><br>Close monitoring of pain and for signs of opioid toxicity is required.<br><br>Alfentanil and fentanyl are the safest opioids of choice in patients with stages 4 or 5 kidney disease (estimated glomerular filtration rate <30 ml/ min/1.73 $m^2$).<br><br>Paracetamol is considered the non-opioid analgesic of choice for mild-to-moderate pain in patients with renal impairment.<br><br>Adjuvant analgesics may require dose adjustment in patients with renal impairment. |

Risk stratification of individual opioids (See Table 14 in Section 2.5.4 and reproduced here)

| Drug | Recommendations in patients with cancer and renal impairment | Comment |
|---|---|---|
| Codeine | If judged appropriate to use, then do so with caution. | Metabolised to morphine sulphate and codeine-6-glucoronide, which accumulate in renal impairment (RI). No clinical studies of use in cancer pain and RI identified. However, there have been reports of severe hypotension, respiratory arrest and profound narcolepsy in patients with advanced RI in the general population. The manufacturer advises that codeine is used cautiously, at a reduced dose, in patients with RI and avoided in patients with severe RI. However, codeine is used in practice in some renal units. |
| Tramadol | If judged appropriate to use, then do so with caution. | Metabolised extensively in the liver. Unmetabolised tramadol and its metabolites may accumulate in RI. No clinical studies identified in cancer pain and RI population but expert opinion suggests that when using weak opioids, tramadol should be used in preference to codeine. The manufacturer recommends that the dosage interval should be increased to 12 hours if CrCl is less than 30ml/min. Modified release preparations should be avoided. In severe RI (CrCl <10ml/min), tramadol is not recommended due to prolonged elimination. |
| Morphine sulphate | If judged appropriate to use, then do so with caution. | Active metabolites produced via hepatic metabolism (morphine-3-glucoronide and morphine-6-glucoronide) accumulate in renal impairment. Studies demonstrate an increased risk of adverse events in renal impairment. |
| Oxycodone | If judged appropriate to use, then do so with caution. | Metabolised to oxymorphone and noroxycodone in liver. Excreted renally. Inconsistent evidence regarding safety in renal impairment. The manufacturer contraindicates its use in severe RI (CrCl <10ml/min). |
| Hydromorphone | If judged appropriate to use, then do so with caution. | Metabolised in the liver to hydromorphone-3-glucoronide. All metabolites excreted renally.<br><br>Evidence for the safety of hydromorphone in renal impairment is inconsistent. However, hydromorphone is used in a number of units that deal with renal impairment frequently, and there are reports of its successful use in such patients, when titrated carefully. |
| Fentanyl | May be used in renal impairment. Opioid of choice, along with alfentanil, in severe RI | Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight. |
| Alfentanil | May be used in renal impairment. Opioid of choice, along with fentanyl, in severe RI | Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight. |
| Buprenorphine | If judged appropriate to use, then do so with caution. | Metabolised to norbuprenorphine and norbuprenorphine-3-glucuronide, which are excreted in the urine; unchanged buprenorphine is mainly excreted in the faeces. Limited amount of evidence for use in RI in general population and cancer population. The manufacturers of the buprenorphine patch suggest no dose changes are required whereas RI is listed as a precaution for the 2mg sublingual tablets. |
| Methadone | If judged appropriate to use, then do so with caution in the specialist setting only | Primarily excreted in the faeces, with 20% excreted unchanged in the urine. No clinical studies identified and pharmacology is complex. |

## The use of opioids in patients with hepatic impairment

The degree of derangement of liver function tests; the extent of clinical evidence of hepatic decompensation; and measures such as the Child-Pugh or Model for End-stage Liver Disease (MELD) scores may be used to determine the severity of hepatic dysfunction, and to predict the likelihood of altered drug metabolism and clearance.

### General measures

The therapeutic index of any opioid is narrower in the setting of liver disease, and opioids should therefore be initiated at lower doses and prescribed with extended dosing intervals.

**Recommendations on the use of analgesics in liver disease** (See Table 17 in Section 2.6.3 and reproduced here)
(Adapted from PANG (19) and Hanna (37))

| Drug | Recommendations in liver disease | Comment |
|---|---|---|
| Codeine | Avoid use | In moderate hepatic impairment, codeine will have unpredictable efficacy and adverse effects. |
| Tramadol | Use with caution<br>Avoid in severe | In moderate hepatic impairment, tramadol will have unpredictable efficacy and adverse effects. If use cannot be avoided, increase the dosage interval. |
| Morphine sulphate | Use with caution | Moderate impairment – use lower doses and extend dosing interval. In severe, hepatic impairment, oral bioavailability may equal that of intravenous. |
| Oxycodone | Use with caution<br>Avoid in severe | Moderate impairment – use lower doses with a minimum dosing interval of 6 hourly for normal release products. |
| Targin® (Oxycodone/ naloxone) | Use with caution<br>Avoid in moderate to severe liver disease | Naloxone component may be systemically absorbed and precipitate pain and opioid withdrawal. |
| Hydromorphone | Use with caution | Dosage reduction necessary. In severe hepatic impairment oral bioavailability may increase significantly. Monitor patient carefully for adverse effects. |
| Fentanyl | Use with caution | Avoid transdermal products. Single doses appear unaltered by liver disease. May be suitable for the treatment of breakthrough pain. |
| Alfentanil | Use with caution | Dosage reduction necessary. |
| Methadone | Not advised | Not advised in moderate liver failure due to the risk of accumulation and fatal adverse effects. |

There is very limited evidence available to evaluate the use of opioids in patients with liver impairment. Liver disease can alter the pharmacokinetics of opioids.

### R 39 Opioids in hepatic impairment

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation*

| | |
|---|---|
| **C** | In advanced liver impairment:<br>Opioids should be used with caution in patients with advanced liver disease. Dosage recommendation should be patient specific and specialist advice sought.<br><br>The transdermal route should be avoided, as drug absorption can be variable and unpredictable.<br><br>Sustained release preparations should be avoided. |

## Non-pharmacological approaches to the management

Along with opioid and non-opioid pharmacological interventions, it is important to consider non-pharmacological interventions which have the potential to control cancer pain and improve quality of life.

**Radiotherapy**

Radiotherapy is an effective and well-tolerated treatment for the management of pain related to bone metastases.

### R 40 Radiotherapy

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **A** | Patients with pain secondary to bone metastases that is difficult to control by pharmacological means alone should be referred to a radiation oncologist for consideration of radiotherapy. |

**Percutaneous cementoplasty**

Percutaneous cementoplasty is an effective and well-tolerated intervention for pain secondary to destructive bone metastases within the spine or pelvis.

### R 41 Percutaneous cementoplasty

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

**Best Practice Point**

The selection and management of patients requiring percutaneous cementoplasty should be carried out in the context of a multidisciplinary team, which may include specialists in radiology, oncology, radiotherapy, orthopaedics, pain management and palliative care.

| | |
|---|---|
| **C** | **41.1** Patients with difficult to control pain secondary to malignant vertebral collapse should be referred for consideration of vertebroplasty, or kyphoplasty. |
| **C** | **41.2** Patients with difficult to control pain secondary to destructive pelvic metastases should be referred for consideration of percutaneous cementoplasty, where this technique is available. |

## Anaesthetic Procedures

### Neuraxial opioids

Opioids can be delivered by the spinal or epidural routes, and may provide analgesia at lower dose than that required for systemic administration. This may be useful where pain is refractory to systemic opioids, or where intolerable side-effects are experienced with systemic opioids. There is, however, limited available evidence regarding the use of neuraxial opioids in the management of cancer pain.

**R 42 Neuraxial opioids**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | Neuraxial opioid therapy for management of cancer pain should be considered where pain is refractory to or intolerable side-effects are experienced with systematic opioids; and should be used only when oral, transdermal, subcutaneous and parenteral options have been exhausted. |

## 2.2 Principles of pain management

### 2.2.1 What is pain?

Pain may be defined in any of the following ways:

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (38).
- Pain is an experience that affects, and is affected by, both the mind and the body. It involves the perception of a painful stimulus by the nervous system and the reaction of a person to this (39).

### 2.2.2 Incidence of pain in cancer

Estimates indicate that 50%-90% of cancer patients experience pain at some stage (24). Cleeland et al studied patients with metastatic cancer receiving oncological treatment in an outpatient setting and reported that pain was experienced by at least 30% in this group (40). Over 80% of cancer patients with advanced metastatic disease have been reported to suffer pain, caused mostly by direct tumour infiltration of surrounding tissues or structures. In addition, side-effects of common cancer treatments may contribute to pain; approximately 20% of pain in cancer patients may be attributed to the effects of surgery, radiotherapy or chemotherapy. Cancer pain may be acute or chronic and should be addressed accordingly (41).

### 2.2.3 Classification of pain

The classification of cancer pain is challenging due to its heterogeneity and complexity. Use of a common classification system to describe cancer pain would improve the translation of results from clinical trials into clinical practice, guide clinical decision-making and improve the treatment of cancer pain (42). However, there is no universally accepted classification system in widespread use. Classification systems commonly include information on pain intensity, quality, localisation and effect on function.

#### 2.2.3.1 Pain Terminology

**Acute pain**

Acute pain is short term pain of normally less than twelve weeks duration (43). Acute pain has a well-defined onset, generally associated with subjective and objective physical signs and with hyperactivity of the autonomic nervous system. Acute cancer pain should be managed by addressing treatment of underlying cause and using analgesic drug therapy (19).

**Chronic pain**

Chronic pain is continuous, long-term pain of more than 12 weeks duration (44). It is described as pain that persists after the time that healing would have been thought to have occurred in pain after trauma or surgery (43). Chronic pain may be associated with significant changes in lifestyle, functional ability and personality. Management is challenging as it requires careful assessment, not only of the intensity and nature of pain, but also of the degree of psychological distress (19).

**Background pain**

Background pain is present for more than 12 hours a day during the previous week, or would be present if the patient was not taking analgesia (45). This pain is also referred to as baseline pain and may be managed with regularly administered slow release analgesic preparations.

**Breakthrough pain**
Breakthrough pain is a transitory exacerbation of pain experienced by the patient with stable and adequately controlled baseline (background) pain. The use of a pharmacological 'rescue' or 'breakthrough' dose of analgesia is widely accepted as the management of breakthrough pain (46).

**Incident pain**
Incident pain is a variation of breakthrough pain, normally precipitated by a movement or action of the patient, or another identifiable precipitant such as a wound dressing change.

**Total pain and multi-dimensional approach to pain assessment and treatment**
In the uni-dimensional approach to pain, all aspects of the pain experience, including use of analgesics and psychological distress, are attributed to the patient's reported pain intensity (47). However, it is increasingly recognised that pain encompasses not only physical aspects, but also:

- Psychological aspects – change in body image and function; fear of pain, or death; feelings of helplessness and dependency; affective components such as mood disturbance and anxiety
- Social aspects – loss of role in family, career or society; feelings of abandonment or isolation
- Spiritual aspects – search for the meaning of the pain and illness; perception of illness as a punishment (48).

Pain must therefore be assessed in the context of these variables (47).

Dame Cicely Saunders, the pioneer of modern palliative clinical practice, defined the concept of total pain as the suffering that encompasses all of a person's physical, psychological, social, spiritual, and practical struggles (48-50). She described pain as a 'key' which unlocks other problems and which requires multiple interventions for its resolution (49).

Some practitioners have broadened this concept to 'total suffering', defined as 'a threat to personal integrity' and encompassing not only physical symptoms, but also threats to the 'intactness' of the person and an impending sense of disintegration of a familiar world (51). Total pain, and suffering, are often under-recognised in the current predominantly biomedical model of care (47).

### *2.2.3.2 Types of pain*

Pain can be grouped into three broad categories

- Nociceptive Pain
- Neuropathic Pain
- Mixed Pain

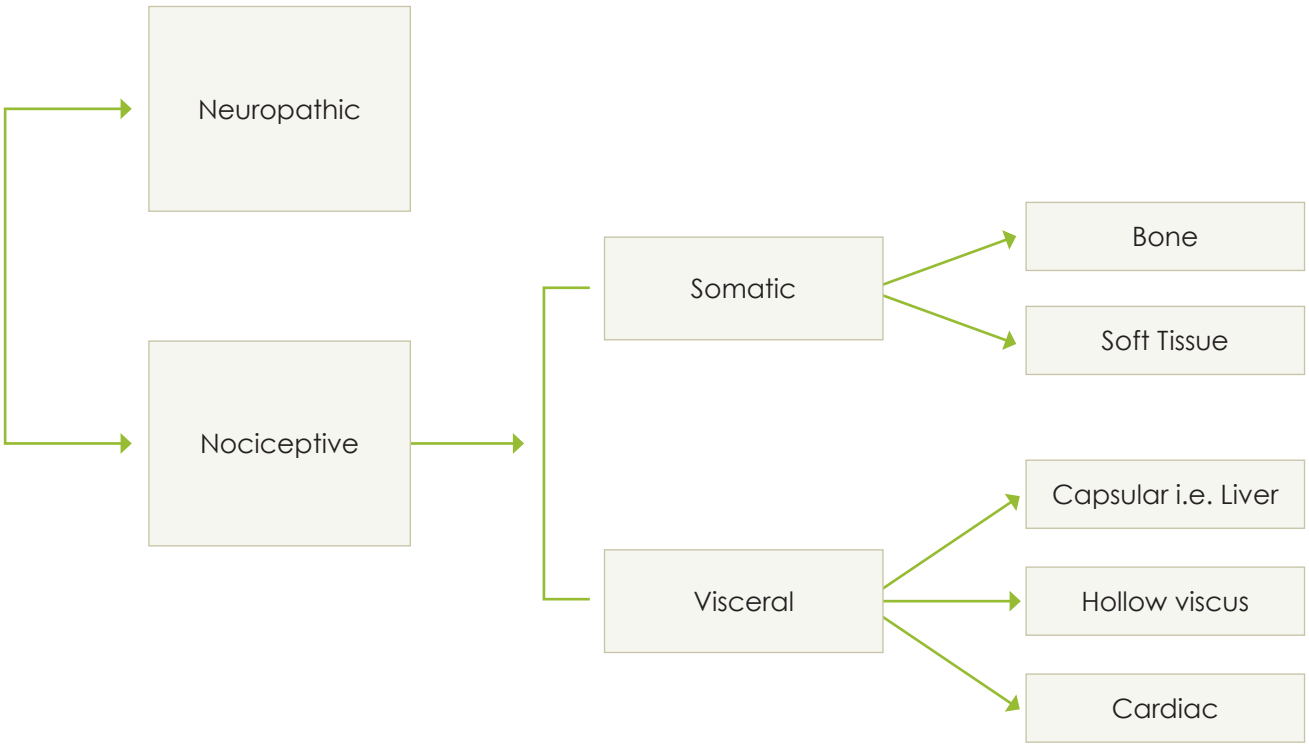



**Figure 1** Classification of pain, adapted from Palliative Adult Network Guidelines (PANG) 2011 (19).

**Nociceptive Pain**

Nociceptive pain is pain that is associated with stimulation of nociceptors. These are sensory receptors that respond to actual tissue damage.

- If these receptors are located in the musculoskeletal system they are referred to a *somatic* nociceptors and the resulting pain as *somatic pain*. Pain that is well-localised, throbbing and pressure-like is probably somatic nociceptive pain, such as pain post-surgery or pain from bone metastases (52).
- If these receptors are associated with internal organs, they are referred to as *visceral* nociceptors and the resulting pain as *visceral pain*. Pain that is described as diffuse, aching, cramping or poorly-localised is frequently visceral pain, secondary to compression, infiltration or distention of abdominal or thoracic viscera (52).

**Neuropathic pain**

Neuropathic pain is pain that is a result of nerve damage to the central or peripheral nervous system. Neuropathic pain is frequently described as shooting, burning or stinging. Up to 40% of cancer-related pain may have a neuropathic mechanism involved (53). It may have associated features indicative of nerve malfunction, such as hypersensitivity, tingling, numbness and weakness in the area of distribution of the affected nerve. Some neuropathic pain terminology includes (54, 55):

- Hyperalgesia: An exaggerated response to noxious stimuli (a stimulus that is normally painful)
- Allodynia: An exaggerated response to an innocuous stimulus (that does not normally provoke pain)
- Paraesthesia: An abnormal sensation, whether spontaneous or evoked
- Dysaesthesia: An unpleasant, abnormal sensation, whether spontaneous or evoked by rubbing or touching
- Neuralgia: Pain in the distribution of a nerve or nerves.

**Mixed Pain**
Many pains have components of both neuropathic and nociceptive elements: this is termed **mixed pain.**

### *2.2.4 Importance of consideration of the psychological aspects of cancer pain*

Pain, especially cancer-related pain, is not a purely nociceptive physical experience, but involves different dimensions such as affect, cognition, behavior and social relations (56). From a psychosocial perspective, cancer pain is challenging for many reasons. Cancer pain is usually treated medically; because of this, healthcare professionals and patients often underestimate the impact of cancer pain on psychological distress and the potential benefits of including psychological treatments to manage cancer pain. For example, cancer pain may raise concerns about disease progression for patients and their families, causing significant anxiety (57).

There have been many studies over the past two decades into the association between cancer pain and psychological functioning. Some of the major findings are as follows:

- Robinson et al (2014) conducted a systematic review of the demoralization syndrome in individuals with progressive disease and cancer. Their findings suggest that demoralization is prevalent in patients with progressive disease or cancer and clinically significant in 13%-18%. Patients who have poorly controlled physical symptoms are at increased risk for demoralization (58). **Level 2a**
- O'Connor et al (2011) performed a multivariate analysis of clinical data from 2768 patients, measuring EORTC quality of life (QOL) and the Hospital Anxiety and Depression Scale (HADS). Cancer pain was found to be independently strongly associated with emotional distress (59). **Level 2a**
- Gerbershagen et al (2008) assessed 115 patients undergoing radical prostatectomy for pain and quality of life measures. Patients with pain in the previous 3 months had higher depression and anxiety scores (HADS) and lower well-being scores, with worse outcomes noted in cancer related pain vs. non cancer related pain (60). **Level 2b**
- Zaza and Baine (2002) performed a systematic review of the literature in relation to cancer pain and psychological factors which included 31 papers. This found a strong correlation between psychological distress and cancer pain (61). In a study of 359 oncology outpatients, those with pain (54.2%) scored significantly higher on all the subscales of the Profile of Mood States (POMS) and had a significantly higher Total Mood Disturbance (TMD) than pain-free patients. More specifically, cancer patients with pain had significantly higher levels of anxiety, depression and anger. Patients with higher pain intensity and longer duration of pain had the highest levels of mood disturbance (62). **Level 1b**
- Strang et al (1997) studied 78 cancer in-patients being treated for cancer-related pain and found that patients with a higher overall mean pain score (i.e. insufficient pain control) or higher mean worst pain score expressed significantly more fear about the future, worries about pain progression and general anxiety that hampered their daily living (63). **Level 2b**

These studies indicate that the cancer pain experience is associated with higher levels of distress, depression, anxiety, fear and negative mood. Various psychological and cognitive behavioural techniques, along with pharmacological intervention, constitute a comprehensive approach to the management of cancer pain (64).

Cancer pain management should be undertaken as part of comprehensive palliative care. Relief of other symptoms, and of psychological, social and spiritual problems, is

paramount. Attempting to relieve pain without addressing the patient's non-physical concerns is likely to lead to frustration and failure (65).

**Recommendation 1 Domains of cancer pain**
**The following are responsible for implementation of recommendation 1:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Cancer pain impacts on a patient's physical, psychosocial and emotional wellbeing. | |
| **Key recommendation** | |
| **A** | Cancer pain management should address the physical, psychosocial and emotional domains of patient care. Addressing the physical aspects of cancer pain alone is insufficient. |

### *2.2.5 Patient involvement in cancer pain management*

The active involvement of patients through the provision of information, instruction and education regarding pain, and pain treatments, is an integral component of pain management strategies (2, 19, 52, 66).

- De Witt et al (1997) performed a randomised control trial of 313 patients to investigate the impact of a pain education program on chronic cancer pain. The study revealed that patient involvement and education resulted in a significantly higher level of patient knowledge, combined with a significant decrease in pain intensity (67). **Level 1b**
- Street at al (2014) performed a randomised controlled trial that tested the effects of a tailored education-coaching intervention on pain control for patients with advanced cancer. Cancer patients who ask questions, express concerns and state preferences about pain-related matters can prompt physicians to change their pain management regimen which may in turn lead to better pain control (66). **Level 1b**
- Adam et al (2015) performed a systematic review of systematic reviews with nested narrative review of randomised controlled trials of educational interventions for cancer pain. They found eight systematic reviews and 34 RCTs of relevance that identified a consistent small to moderate reduction in pain intensity, with interventions targeting professionals also showing some improvement in their knowledge (although how this is translated to patient benefits is as yet unclear). The review concludes that cancer pain educational interventions can improve pain outcomes. They are complex heterogeneous interventions which often contain a combination of active components (68). **Level 1a**

**Recommendation 2 Patient involvement in cancer pain management**
**The following are responsible for implementation of recommendation 2:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Involving and educating patients about their pain management improves patient understanding and can decrease pain intensity. | |
| **Key recommendation** | |
| **B** | Patients should be given appropriate information about their pain, and pain management, and be encouraged to participate in their treatment plan. |

### *2.2.6 Aims of cancer pain management*

The aims of managing cancer pain are to (69):

- Achieve a level of pain control that is acceptable to the patient
- Assess pain and evaluate the effectiveness of management promptly
- Be aware of the components of total pain
- Relieve pain at night, at rest and on movement
- Provide patients and their carers with up-to-date information on using pain relieving drugs
- Support and encourage carers.

High quality pain management includes appropriate assessment including; screening for the presence of pain; completion of a comprehensive initial assessment when pain is present; and frequent reassessments of pain responses to treatment. Interdisciplinary collaborative care-planning is important, including patient and family input. Appropriate treatment that is efficacious, cost-conscious, culturally and developmentally appropriate and safe is required, as is access to specialty care as needed (70).

### *2.2.7 Pain Assessment*

Systematic assessment of cancer pain is an essential component in formulating an appropriate and effective treatment plan (19). A comprehensive assessment of pain should consider the following domains (2):

- Physical effects/manifestations of pain
- Functional effects (interference with activities of daily living)
- Psychosocial factors (level of anxiety, mood, cultural influences, fears, effects on interpersonal relationships)
- Potential modulators of pain expression such substance use, alcohol, and delirium (71)
- Spiritual aspects

Luckett et al (2011) performed a systematic review and synthesis of qualitative studies concerned with cancer pain assessment and management. They report barriers as being reluctance to report pain, lack of caregiver understanding of pain, insufficient recognition of caregiver contributions by health professionals, and widespread misconceptions about opioids. Assessment should be individualised according to patient and family needs, priorities, and circumstances (72).

**Level 2a**

Pain is inherently subjective; therefore the patient should be the prime assessor of his or her pain (where competent and able to communicate) (2, 19, 69, 73). Health professionals have been shown to underestimate the level of pain a patient is experiencing, whilst family members may overestimate pain in their loved ones (74-76). **Level 5** **Level 4**

Certain principles should be adhered to when evaluating all cancer patients who complain of cancer pain (44): **Level 5**

- Believe the patient's complaint of pain
- Take a careful history of the pain complaint, to place it temporally in the patient's cancer history
- Assess the characteristics of each pain including:
  - The site of the pain
  - The type of the pain
    - Nociceptive, neuropathic, mixed
  - Exacerbating and relieving factors
  - The temporal pattern
    - Acute, subacute, chronic, baseline, intermittent, breakthrough or incident
  - The exact onset
  - Associated symptoms and signs
  - Interference with activities of daily living
  - Impact on the patient's psychological state
  - Response to previous and current analgesic therapies
- Perform a thorough clinical examination including neurological examination
- Evaluate the psychological state of the patient:
  - This is important as a patient's levels of anxiety and depression can have a significant impact on their pain experience, which in turn can further impact on the patient's psychology
  - Determine what the significance of the pain to the patient is. Do they feel that it represents a deterioration of their underlying cancer?
- Evaluate the spiritual impact of the pain:
  - Chronic pain and cancer pain may impact on a patient from a spiritual perspective. The spiritual domain involves (77):
    - Meaning
    - Hope
    - Love and relatedness
  - Some of the spiritual interventions that may result from this include presence, attentive listening, acceptance and judicious self-disclosure, which may play a role in promoting comfort and diminishing pain.

**Recommendation 3 Patient assessment of cancer pain**
**The following are responsible for implementation of recommendation 3:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>The cornerstone of comprehensive pain assessment is the taking of a detailed patient history and the performance of a thorough physical examination. The psychological and spiritual impact of a patient's pain should also be considered.<br><br>Pain is a subjective experience. | |
| **Key recommendation** | |
| **C** | Systematic assessment of cancer pain including physical, psychological, and spiritual domains is essential.<br><br>The patient should be the prime assessor of his or her pain. |

### *2.2.7.1 Pain and symptom assessment tools*

Symptom assessment tools can provide valuable information as part of both the initial and ongoing assessment of a patient's symptoms including pain. Symptom assessment tools that focus solely on the assessment of pain are termed 'pain assessment tools'. While pain and symptom assessment tools provide a method by which patients symptoms can be comprehensively assessed, there is no international consensus on which is the gold standard tool for the assessment of cancer pain (2). **Level 5**

**Pain assessment tools**
Different types of pain assessment scales exist. Pain tools may be considered to be unidimensional (such as visual analogue scales (VAS), numerical rating scales (NRS) or categorical scales (verbal rating scales, VRS) or multidimensional (78, 79). **Level 5**
Multidimensional tools assess both severity of pain and its impact on the patient. A variety of numerical cut points have been suggested to categorise pain as mild, moderate or severe. However, a recent systematic review (80) advises that evidence is limited on cut points, and cautions against making a strong recommendation for cut points. The authors found best evidence for a cut point of 5 for moderate pain and 7 for severe pain. **Level 2b**

Examples of multidimensional assessment tools include:
- The Memorial Pain Assessment Card (81)
  - The Memorial Pain Assessment Card utilises a verbal rating scale for intensity (mild, moderate, strong etc.) and three visual analogue scales (for intensity, relief, and mood).
- The Brief Pain Inventory (82)
  - The Brief Pain Inventory assesses the history, intensity and quality of the patient's pain combined with a number of numerical scales and includes the functional impact of the pain on the patient's life.
- The McGill Pain Questionnaire (83-85)
  - The McGill Pain Questionnaire assesses multiple dimensions of pain and has global scores and subscales. The tool includes a drawing for pain localisation and has 102 pain descriptors in total. A short-form McGill Pain Questionnaire was developed in 1987, which contains fifteen descriptors.

Pain assessment tools specific to breakthrough cancer pain, which is identified as having unique temporal characteristics, are in the process of being developed and validated (86).

The use of information and communication technology (ICT) in the assessment of pain and other symptoms in the cancer setting is at an early stage of development, with early indications of patient acceptance and effectiveness of the approach (87).

**Symptom assessment tools**

Studies demonstrate a significant correlation between pain, depression, fatigue and other symptoms commonly seen in a cancer setting; these are known as 'symptom clusters' (8). Many multidimensional symptom assessment tools have been developed. In one study looking at the number of symptom assessment tools available, 21 symptom assessment tools were identified, with another 28 in existence that examine symptom prevalence and interrelations (88). Examples of multidimensional symptom assessment tools are:

- Memorial Symptom Assessment Scale (89)
- Rotterdam Symptom Checklist (90)
- M.D. Anderson Symptom Inventory (91)
- The Edmonton symptom assessment scale (Appendix XII), or ESAS, was developed by Bruera et al in 1991 and merits particular attention because of widespread use. It is an 11-point numerical rating scale used to rate nine symptoms with an optional tenth symptom nominated by the patient. The presence and severity of each symptom is scored from 0 to 10. The scoring process can be completed by the patient alone or with the help of a caregiver. If the patient is unable to complete the exercise the care-giver can do so on their behalf (92, 93). The ESAS has been validated in advanced cancer patients in many different populations.
    - Recent studies suggest that, whilst the ESAS is a reliable tool, its validity may be more restricted, and its use requires a sound clinical process to help interpret scores and to give them an appropriate level of attention (94). A fifteen year retrospective review of ESAS validation studies found that the use of varying instrument formats and limited psychometric evidence supported the need for further ESAS validation studies, most notably the inclusion of patient involvement (95). **Level 2a**

It should be noted that while the use of pain and symptom assessment tools may confer benefits, some concerns about burden also exist, especially for populations with advanced disease (78, 96-99). In addition, not all studies concur that proxy ratings of patients' symptomatology are an accurate reflection of patient distress (100-102). Thus, the ESAS and other multidimensional tools may become difficult to implement in end of life situations and may be of limited clinical assistance. **Level 2b**

**Psychological distress assessment tools**

Psychological distress should be screened for as part of the continuous assessment of cancer pain. There are a number of assessment tools in existence, such as the Hospital Anxiety and Depression Scale (103), the Beck Depression Inventory (104) and the Self-rating Depression Scale (SDS) (105).

Asking the patient the single question '*are you depressed?*' may also be effective for screening for the presence of depression. Chochinov (1997) performed semi-structured diagnostic interviews on 197 cancer patients receiving palliative care and found that asking this question was a valid method of screening for depression (106). Furthermore, Payne et al (2007) performed a prospective study on 167 consecutive admissions to a specialist palliative care unit in Ireland and found that asking two questions: '*Are you depressed?*' and '*Have you experienced loss of interest in things or activities that you would normally enjoy?*' demonstrated a high sensitivity and specificity, with a low false negative, in screening for depression (107). Mitchell et al (2008) performed a Bayesian meta-analysis (literature review) of these *one-question* or *two-question* screening tools and found the 'two question' method to be significantly more accurate than a single question (108). However, clinicians should not rely on these simple questions alone and should be prepared to follow with more in-depth assessment as required (109).

**Level 2a**

**Spiritual assessment tools**

The spirituality of an individual includes meaning, relatedness, hope and forgiveness (73). Many patients believe spirituality plays an important role in their life, that there is a positive correlation between a patient's spirituality and their health outcomes and that they would like physicians to consider these factors in their medical care (110). A spiritual assessment may be conducted using the HOPE spiritual assessment tool (109).

**Level 5**

The HOPE questions are as follows:

- **H** - sources of hope, strength, comfort, meaning, peace, love and connection;
- **O** - the role of organised religion for the patient;
- **P** - personal spirituality and practices;
- **E** - effects on medical care and end of life decisions.

### *2.2.7.2 Quality of care assessment tools*

**The STAS and the POS (111)**

The Palliative Care Outcome Scale (POS) (Appendix XIII) and the Support Team Assessment Schedule (STAS) are outcome measures assessing quality of care in palliative care patients. The STAS was originally developed in 1986 as a standardised measurement tool to evaluate the work of palliative care support teams (112). It consists of 17 items, to be rated from 0 (best) to 4 (worst) by a professional caring for the patient (113). These items measure patient symptoms, anxiety and insight, family anxiety and insight, quality of communication with healthcare professionals and carers, and need for practical support. Extra items, such as additional symptoms, can be added to the existing instrument (111).

As a further development of the STAS, the POS was developed in 1999 for use with advanced cancer patients (114). The POS was designed to advance outcome measurement by evaluating many of the same outcomes as STAS and other current scales (e.g. McGill Quality of Life Questionnaire) while also including a subjective patient element to the measurement of outcomes. POS is therefore a patient reported outcome measure when the patient version of POS is used. POS consists of ten items which are scored from 0 (best) to 4 (worst), and which assess physical symptoms, emotional, psychological and spiritual needs, and provision of

information and support. The last question gives patients the opportunity to list their main problems. POS consists both of a patient and a staff version, which differ only in the provision of an additional item addressing the patient's performance status in the staff version. In addition, a carers' version has also been developed. Originally, all items were intended to assess the patient's state over the preceding three days, however longer periods have been used in subsequent research. When timed, the questionnaire has been reported to take no longer than 10 minutes to complete by staff or patients (114).

**Recommendation 4 Assessment tools**
**The following are responsible for implementation of recommendation 4:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>A number of assessment tools exist in relation to the physical, psychosocial and spiritual domains of cancer pain. | |
| **Key recommendation** | |
| **D** | The use of pain and other symptom assessment tools should be considered as part of the comprehensive ongoing evaluation of cancer patients. |

### *2.2.8 Pain assessment in patients with cognitive impairment*

Patient self-reporting is the gold standard of pain assessment (115). However, self-reporting of pain and other symptoms may not be feasible in patients who are unable to verbalise, for example those who are critically ill, unconscious, dying or who have cognitive impairment. In 2006, the American Society for Pain Management published guidelines for pain assessment in non-verbal patients (116). These guidelines relied on a systematic approach to patients in these situations as follows:

**Level 5**

1. Use the hierarchy of pain assessment tools
   - Self-report: attempts should be made to obtain self-report from all patients
   - Search for potential causes of pain, such as pathologic conditions or procedures known to cause pain (e.g. surgery, wound care, positioning).
2. Observe patient behaviours: Non-verbal cues as to patient discomfort may be (117)
   - Facial expression: grimacing, rapid blinking, frowning
   - Negative vocalisation: groaning, aggressive behavior, sighing
   - Body language: tense posture, guarding, fidgeting
   - Changes in activity patterns of routines: sleep patterns, appetite changes, wandering or pacing
   - Changes in interpersonal interactions: withdrawn, combative, refusing care
   - Mental status changes: increased confusion, irritability, agitation.
3. Surrogate reporting: by family members, parents, caregivers. Discrepancies exist between self-report of pain and external observer judgments of pain severity; these occur across varied raters (e.g. physician, nurse, family, aides) and settings (e.g. inpatient, outpatient, acute care, long-term care). Thus, judgments by caregivers and clinicians may not be accurate reflections of the severity of pain experienced by non-verbal persons and should be combined with other evidence when possible. A multifaceted approach is recommended, that combines direct observation, family/caregiver input and evaluation of response to treatment.

4. Attempt an analgesic trial: A trial with analgesia should be undertaken if there is evidence of pathologic conditions or procedures that are likely to cause pain, or if there are unresolved pain behaviours after attention has been paid to basic needs and comfort measures. Analgesia is provided with reference to the estimated intensity of the patient's pain based on the patient's pathology and analgesic history.
5. Establish an ongoing procedure for pain assessment (118): Assessment approaches and pain indicators should be documented in a readily visible and consistent manner, that is accessible to all healthcare providers involved in the assessment and management of pain (119).

**Behavioural assessment tools**
There are a number of behavioural pain assessment tools for elderly patients with severe dementia (2), such as the DOLOPLUS 2, the Pain Assessment Checklist for Seniors with Limited Ability to Communicate [PACSLAC) and the ADD (The Assessment of Discomfort in Dementia Protocol). These tools are at varying stages of development, but may be useful as part of a multifaceted approach to pain assessment in the cognitively impaired patient.

**Physiological factors**
Little research supports the use of vital signs (e.g. heart rate, blood pressure, respiratory rate) as a reflection of patient pain. The absence of increased signs does not reflect the absence of pain (120).

**Recommendation 5 Pain assessment in patients with cognitive impairment**
**The following are responsible for implementation of recommendation 5:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>In patients with cognitive impairment, a systematic approach to pain assessment including the use of pain assessment tools, behavioural observations, surrogate reporting and analgesic trials is recommended. | |
| **Key recommendation** | |
| **D** | Pain assessment in the cognitively impaired should involve self-reported pain scales where appropriate. Observational pain rating scales and behavioural assessment tools should be considered for those who cannot complete a self-assessment scale. |

### *2.2.9 Treatment of cancer pain*

Once a comprehensive assessment of a patient's pain has been made including the physical, psychosocial and emotional domains, the various treatment approaches should be considered prior to the formulation of a treatment plan.

The World Health Organisation (WHO) first published *Cancer Pain Relief* in 1986 (121), designed to be a simple, intuitive and accessible guide to the management of cancer pain that would be applicable and useful whatever the language, culture, economy, country and clinical setting. The guidelines, based on a three-step analgesic ladder, are widely accepted and have had significant clinical and educational impact across the globe (122). In 1990, the WHO outlined a general approach to pain management, as follows (65):

**Table 3** Approaches to pain management in cancer patients, (adapted from Cancer Pain Relief, 2nd ed. Geneva: WHO, 1996 (121))

| Approaches to pain management in cancer patients | |
|---|---|
| **Psychological Approaches**:<br>• Understanding<br>• Companionship<br>• Cognitive behavioural therapies | **Interruption of pain pathways:**<br>• Local anaesthetic agents<br>• Neurolytic agents |
| **Modification of pathological processes:**<br>• Radiotherapy<br>• Hormone therapy<br>• Chemotherapy<br>• Surgery | **Modification of daily activities/immobilisation:**<br>• Rest<br>• Cervical collar<br>• Plastic splints or slings<br>• Orthopaedic surgery |
| **Drugs:**<br>• Analgesics<br>• Antidepressants<br>• Anticonvulsants<br>• Anxiolytics<br>• Neuroleptics | |

### *2.2.10 The World Health Organisation analgesic ladder*

The WHO analgesic ladder (figure 2) has been extensively validated (5, 123, 124) and its use debated in the literature (125-131). It is estimated that between 71% and 100% of patients achieve adequate analgesia for cancer pain when the WHO approach is used appropriately (5, 123, 126, 132-135). A small proportion of patients (10-30%) do not respond to morphine sulphate or experience intolerable side-effects (124, 136). The WHO guideline should be viewed as a framework of principles that allow flexibility in the choice of analgesics. It has played a critical role in the dissemination of the fundamental therapeutic and caring principles indispensable to the treatment of cancer pain globally (130) and facilitating the acceptance of opioid use worldwide (131).

**Level 1b**

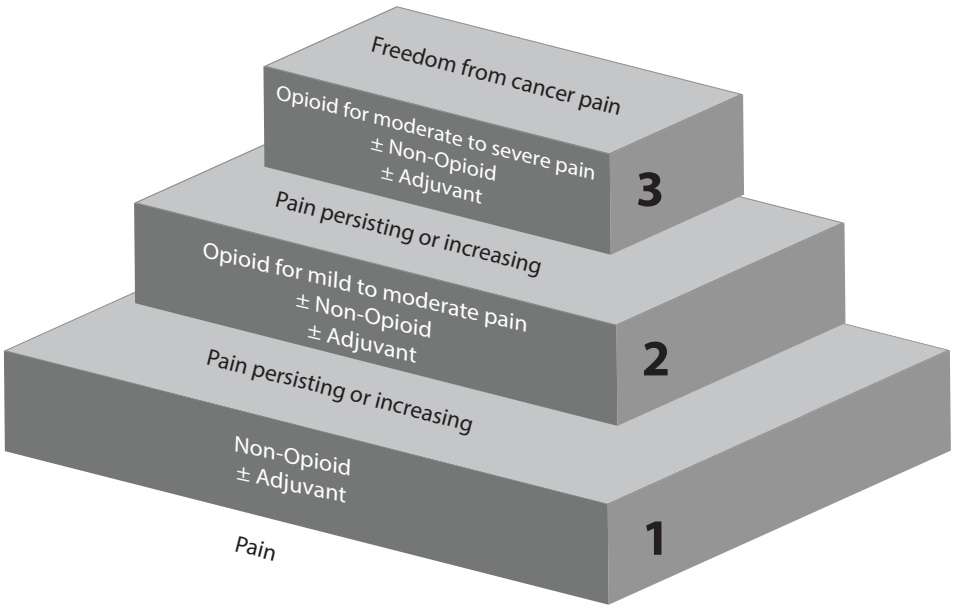



**Figure 2** World Health Organisation analgesic ladder from World Health Organisation. Cancer Pain Relief, 2nd ed. Geneva: WHO, 1996 (121)

The fundamental principles of the WHO document are as follows (121, 137):

1. Oral administration of analgesics:
   The oral form of medication should be used whenever possible. Ideally, two types of formulations are required: normal release (for dose titration) and modified release (for maintenance treatment) (138, 139).
2. Analgesics should be given at regular intervals, taking into account the duration of the medication's efficacy (pharmacokinetics). This will ensure a steady level of analgesia in the patient's bloodstream and reduce the need for breakthrough analgesia.
3. Analgesics should be prescribed according to the degree of pain, as indicated by the WHO ladder.
4. Dosing of pain medication should be adapted for the individual.
   - Every patient will respond differently to analgesic regimens and there is no standardised dosage for the treatment of pain
5. Analgesics should be prescribed with a constant concern for detail.

In summary:

- By the mouth
- By the clock
- By the ladder
- Individual dose titration
- Attention to detail

Thus, medication is prescribed according to pain severity and the accordingly appropriate 'step' on the ladder.

#### *2.2.10.1 How to use the WHO analgesic ladder*

A patient's pain severity should be regularly assessed and the appropriate analgesia prescribed according to the analgesic ladder; the severity of pain determines the strength of analgesia required, whilst the type and cause of pain will influence the choice of analgesic used (2). For a patient with chronic pain, both regular and breakthrough analgesia must be prescribed.

- Collins et al (1997) performed a study on the Visual Analogue pain intensity Scale (0-100mm), using data from 1080 patients enrolled in RCT trials with analgesics (140). Of patients reporting moderate pain, 85% scored over 30mm on the corresponding VAS. For those reporting severe pain, 85% scored over 55mm. Similar correlations have been found in other studies relating categorical rating of pain to visual analogue scales (141, 142); thereby a transference of a patient's pain score can be made to the analgesic ladder (2). **Level 1b**

**Table 4** How to use the WHO Analgesic Ladder (adapted from SIGN Guideline (2))

| WHO analgesic ladder | Score on numerical rating scale | Analgesic of choice |
|---|---|---|
| Step 1:<br>mild pain | 1 to 2<br>out of 10 | Non-opioid (Paracetamol/ NSAID)<br>+/- Adjuvant |
| Step 2:<br>mild to moderate pain | 3 to 6<br>out of 10 | Weak opioid (Codeine/ Tramadol*)<br>+/- Non-opioid<br>+/- Adjuvant |
| Step 3:<br>severe pain | 7 to 10<br>out of 10 | Strong opioid (Morphine sulphate/Oxycodone/ Hydromorphone/ Fentanyl)<br>+/- Non-opioid<br>+/- Adjuvant |

* Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. See recommendation 7.

### *2.2.10.2 Use of analgesic medications, as described by the WHO analgesic ladder*

The WHO analgesic ladder refers to classes of drugs (such as non-opioids, opioids for mild to moderate pain, opioids for moderate to severe pain, adjuvants) (2). This allows clinicians to maintain a level of flexibility when prescribing analgesics, cognisant of the wide global disparity in equitable access to pain medications (143, 144). Some examples of the more commonly used drugs available in Ireland are as follows:

**Table 5** Commonly used drugs for the management of cancer pain

| Non-opioids: | Opioids for mild to moderate pain: |
|---|---|
| • Paracetamol<br>• Non Steroidal Anti Inflammatory Drugs:<br>o Ibuprofen<br>o Diclofenac sodium | • Codeine phosphate<br>• Dihydrocodeine<br>• Tramadol |
| **Adjuvant Medications:** | **Opioids for moderate to severe pain:** |
| • Corticosteroids<br>• Anti-depressants<br>• Anti-epileptics<br>• Anti-spasmodics<br>• Benzodiazepines<br>• Bisphosphonates | • Morphine sulphate<br>• Oxycodone<br>• Hydromorphone<br>• Fentanyl<br>• Buprenorphine<br>• Methadone |

#### 2.2.10.3 Debate regarding the WHO analgesic ladder

The clinical usefulness of step two has been questioned (145) with the argument that the earlier introduction of a strong opioid is more appropriate. Tassarini et al (2011) undertook a systematic review to analyse the evidence supporting the widespread use of modified analgesic ladders (146).

- A meta-analysis was performed of four trials comprising 288 patients, of which 88 were treated with the standard three-step approach and 200 were treated with a modified two-step ladder.
- The level of evidence was low or very low for all the trials, resulting in a low strength of the final recommendations.
- Methodological limitations in trial design and conduct, and trial heterogeneity, meant that it was impossible to assess the risk / benefit of the novel two-step approach compared to the standard approach.

**Level 1b**

**Recommendation 6 The World Health Organisation (WHO) Cancer Pain Relief guidance**
**The following are responsible for implementation of recommendation 6:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding**<br>The WHO analgesic ladder has been extensively validated and shown to be effective in the management of pain in the majority of cancer patients. | |
|---|---|
| **Key recommendation** | |
| **C** | Cancer patients should have their pain managed in accordance with the World Health Organisation (WHO) Cancer Pain Relief guidance. |

## 2.3 Opioids

### 2.3.1 Choice of opioid

#### 2.3.1.1 Opioids for mild to moderate pain

The use of a three-step analgesic ladder has represented the standard of the treatment of cancer pain for over 25 years. It has been suggested that the role of weak, or step two, opioids may be negligible, or even deleterious as the use of weak opioids may lead to a period of uncontrolled pain, and a delay in titration to effective strong opioids (146). To avoid this possible misinterpretation of the ladder, it is imperative that the clinician selects the strength of opioid analgesic according to the current severity of pain (147).

**Codeine phosphate**

Codeine (methylmorphine sulphate) is an opium alkaloid, used as a step two analgesic for the treatment of mild to moderate cancer pain. Oral bioavailability is 40%, with most of the drug metabolised through conjugation to codeine-6-glucuronide. However, the chief analgesic activity of codeine results from its action as a pro-drug of morphine sulphate; 2-10% of codeine is metabolised to morphine sulphate via CYP2D6 (148). CYP2D6 enzyme inhibitors or genetic polymorphisms can reduce morphine sulphate production thus affecting patient analgesic responses. Approximately 7% of Caucasian people, 3% of black people and 1% of Asian people have poor or absent metabolism of codeine, resulting in poor or absent analgesic effect (2).

**Level 5**

Codeine is available in tablet form or as a syrup, and although an injectable form does exist, it is not generally recommended (148). Codeine exhibits a '*dose ceiling*' effect, above which there is no evidence of additional analgesic effect (149). Further titration above this however is associated with an increased risk of side-effects (2). The upper limit of codeine intake should therefore be limited to a maximum of 240mg per day (150).

Straube et al (2014) performed a Cochrane systematic review of randomised, double-blind, controlled trials using single or multiple doses of codeine, with or without paracetamol, for the treatment of cancer pain (151).

- Fifteen studies including 721 participants were identified. Only a small amount of data in studies that were both randomised and double-blind was identified. Studies were small, of short duration, and most had significant shortcomings in reporting.
- Twelve studies used codeine as a single agent and three combined it with paracetamol. Most studies used codeine at doses of 30 mg to 120 mg.
- Of the 10 placebo-controlled studies included in this review, nine demonstrated the superiority of codeine (in one instance codeine plus paracetamol) compared with placebo in the treatment of cancer pain.
- Although a number of different drugs or combinations of drugs were compared with codeine, no two studies made the same comparison, and the numbers involved were too small to draw any firm conclusions.
- The authors conclude that the available evidence indicates that codeine is more effective against cancer pain than placebo, but with increased risk of nausea, vomiting, and constipation. Uncertainty remains as to the magnitude and time-course of the analgesic effect and the safety and tolerability in longer-term use (151).

**Level 1b**

**Dihydrocodeine**

Dihydrocodeine is a semi-synthetic analogue of codeine which has equianalgesic potency to codeine when administered orally, but appears to have a narrow therapeutic index with a higher incidence of adverse effects at a 60mg dose (44).

**Tramadol**

Tramadol is a synthetic centrally-acting analgesic with both non-opioid and opioid properties (148). It is a step two opioid for the treatment of mild to moderate cancer pain. Oral bioavailability is 65-75% and it is metabolised in the liver to an active substrate, O-desmethyltramadol (148). It is available in oral and injectable forms.

- Tassinari et al (2011) conducted a meta-analysis with the aim of analysing and classifying the evidence supporting the use of tramadol as an alternative to placebo or codeine / paracetamol in the second step of the analgesic ladder in mild to moderate cancer pain never treated with opioids (over placebo or other opioids in the management of mild to moderate cancer pain) (146).
  - All randomised clinical trials, prospective clinical trials, and patient series comparing oral tramadol with placebo, codeine, or other opioids were included in the review.
  - 14 papers were identified (eight RCTs, six prospective cohort trials) comprising 1810 patients. Eight randomised trials compared tramadol with other opioids, placebo, or the rectal route of administration. Neither of the two trials comparing oral tramadol with codeine or hydrocodone had the statistical power to demonstrate either equivalence or superiority of tramadol, and no definitive data could be extracted to define a comparative profile of oral tramadol with codeine/paracetamol. None of the six cohort trials added any data to that extracted from the randomised trials. **Level 1b**
  - The authors concluded that, while tramadol emerged as an active and well-tolerated drug, no definitive data was found to suggest its superiority in comparison with codeine/paracetamol, or other opioids. The data supporting the role of oral tramadol as an alternative to paracetamol/ codeine is insufficient, and the doubts about the role of tramadol are stronger than any evidence to support its use in preference to paracetamol/ codeine.

In relation to the multi-modal pharmacology of tramadol as both a weak opioid antagonist and a serotonin-noradrenaline reuptake inhibitor, a systematic review and meta-analysis examined the pharmacological management of neuropathic pain (in both the cancer and non-cancer settings). This found moderate quality of evidence for the use of tramadol for neuropathic pain (152). **Level 1a**

**Tapentadol**

Tapentadol is a mu-opioid receptor agonist and noradrenaline reuptake inhibitor (153, 154).

- Kress et al (2014) performed a randomised control trial to assess the efficacy and tolerability of tapentadol (prolonged release) (PR) compared with placebo in 496 cancer patients. Based on results obtained during titration, tapentadol PR was found to provide comparable efficacy to that of morphine sulfate (controlled release) (CR) (40-100 mg bd). Results obtained during maintenance indicate that tapentadol PR (100 – 250 mg bd) is effective compared with placebo for managing moderate to severe chronic malignant tumour-related pain (155, 156). **Level 1b**
- In a brief report, Mercadante et al (2014) reported on an open labelled, prospective study in a convenience sample of 30 cancer patients admitted to an acute palliative care unit in Italy. The study found tapentadol to be a flexible alternative for patients already pre-treated with strong opioids (minimum of 60 mg of oral morphine equivalent), however 10 patients were lost to follow up. These preliminary findings need to be confirmed with well-constructed prospective and comparative studies (157). **Level 4**
- Imanaka et al (2013) performed a phase 3 study to evaluate the efficacy and safety of tapentadol (extended release) (ER) compared with oxycodone (controlled release) (CR) for the management of moderate to severe, chronic malignant tumor-related cancer pain. 343 patients were randomised. The authors proved the analgesic efficacy of tapentadol was non-inferior to oxycodone, with good tolerability and a better gastrointestinal tolerability profile (158). **Level 2b**

- Mercadante and Ferrera (2012) describe a single case report of successful opioid rotation from methadone to tapentadol, in a patient with multiple myeloma (159). They note the current absence of any data to guide dose conversion ratios, other than comparative studies (155). **Level 5**

**Combination medications for mild to moderate pain (Step 2 WHO analgesic Ladder)**

Codeine/paracetamol combinations have been identified as a useful option in the second step of the analgesic ladder (146). It has been shown that a combination of codeine 60mg / paracetamol 1g is more effective than paracetamol alone, but studies have shown no benefit with a combination of codeine 8mg / paracetamol 1g when compared to paracetamol alone (2). **Level 5**

**Recommendation 7 Weak Opioids**

**The following are responsible for implementation of recommendation 7:**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding** | |
|---|---|
| Codeine, dihydrocodeine and tramadol are examples of weak opioids that are commonly prescribed for use at step two of the WHO analgesic ladder. There is an evidence base to support the use of codeine and codeine/paracetamol in cancer pain. There is insufficient evidence to support the use of oral tramadol or tapentadol in preference to codeine/paracetamol for mild to moderate cancer pain. | |
| **Key recommendation** | |
| **C** | Weak opioids may be used in the treatment of mild to moderate pain. They may be used in conjunction with a non-opioid analgesic. Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. |

### *2.3.1.2 Opioids for moderate to severe pain*

Morphine sulphate, oxycodone, hydromorphone, buprenorphine and fentanyl are examples of 'strong opioids' that are commonly prescribed for use at step 3 of the WHO ladder. They may be prescribed along with paracetamol or a non-steroidal anti-inflammatory medication, or an adjuvant medication.

The choice of strong opioid should take into account efficacy, safety and flexibility of dosing (139). **Level 2b**

Oral morphine sulphate has been considered for 25 years to be the drug of choice for the treatment of moderate to severe cancer pain (160). This is due to its historical background, the variety of clinical experience associated with its use, well established efficacy and safety data (5), low cost, and issues concerned with opioid availability and access globally. However, since the publication of the second edition of the WHO's Cancer Pain Relief strategy, many alternative opioids are now available for use and morphine sulphate itself is obtainable in a variety of new formulations and multiple dose sizes (139). Given these considerations, Caraceni et al (2011) performed a systematic review to evaluate the evidence that oral morphine sulphate continue to be recommended as the first choice opioid in the treatment of moderate to severe cancer pain (160). **Level 1a**

- The available evidence suggests that oral morphine sulphate, hydromorphone, oxycodone and methadone offer similar pain relief in this patient population, with a similar pattern of side-effects (160). **Level 1a**
- Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients (161) (see section 2.3.2.3).

**Combination opioid therapy**

Fallon et al (2011) performed a systematic review examining the evidence for using two strong opioids simultaneously, so called "combination opioid therapy" (162). Currently there is a significant gap between the basic scientific work, which potentially supports a role for combination opioid therapy, and clinical practice where combination therapy is used; the available evidence is very limited and of low quality. As such, there is insufficient evidence at present to support the use of combination opioid therapy. **Level 2a**

**Morphine sulphate**

Morphine sulphate is an opioid analgesic used for the treatment of moderate to severe cancer pain. Its effects are mediated through specific opioid receptors found in the CNS and peripherally. Morphine sulphate appears to have no clinical ceiling effect for analgesia. It is metabolised primarily in the liver into the active metabolites morphine sulphate-3-glucuronide (M3G) and morphine sulphate-6-glucuronide (M6G) (148). These metabolites contribute to toxicity, particularly in patients with renal impairment.

The oral route of administration is favoured for reasons of patient acceptability and preference. However, the systemic availability of morphine sulphate by the oral route is poor (35%, ranging from 15-64%) (148) and this can lead to an unpredictable onset of action and great individual variability in dose requirements and responses (163).

- A qualitative analysis of 18 studies, comprising over 2053 patients, was performed by Caraceni et al in 2011 (160). Many of the included studies had significant methodological limitations and were particularly limited by patient attrition. Five RCTs which compared morphine sulphate to either oxycodone or hydromorphone, in patients already shown to be responsive to morphine sulphate, failed to show any difference in efficacy (160, 164-167). Further RCTs comparing morphine sulphate with fentanyl, (168, 169) and with methadone (160, 170) similarly failed to show any difference in efficacy. The available evidence demonstrates that the efficacy and tolerability of morphine sulphate, oxycodone, hydromorphone and methadone are equivalent, and these agents are all valid choices as first and subsequent choice opioids for moderate to severe cancer pain. However, due to methadone's complex pharmacokinetic profile, it should be used only under specialist guidance (160). **Level 1b**
- Riley et al (2015) performed a randomized , open labelled, controlled trial (n=200) and found no difference in response rate or adverse reaction scores of morphine compared to oxycodone. When both opioids were available, a 95% cancer pain response was documented (171). **Level 2a**

**Combination preparations**

Morphine sulphate / cyclizine combination injections (Cyclimorph®) should not be used in the cancer pain setting as the ceiling dose of cyclizine of 150mg will be quickly reached in uncontrolled pain (19). **Level 5**

**Oxycodone**

Oxycodone is a full opioid agonist for the treatment of moderate to severe cancer pain with similar properties to morphine sulphate (2). It is metabolised principally to noroxycodone via CYP3A4, with a smaller amount metabolised to oxymorphone

via CYP2D6 (148). It is the parent drug however which provides the analgesic effect (172). Taken orally, oxycodone has a more predictable bioavailability (75%) than morphine sulphate (148). It is thus more potent than oral morphine sulphate, whilst parenteral bioavailability is similar (see section 2.2.5). Oxycodone is available in oral formulations, by tablet or liquid, and by injection. It is also available in a fixed-ratio combined oral formulation with naloxone.

- King et al (2011) evaluated the evidence for the use of oxycodone in adult cancer pain through a systematic review (173). The evidence was graded as high quality, on the basis of a well-conducted meta-analysis of 29 studies including 14 RCTs. They found no evidence of a significant difference in efficacy or tolerability of oxycodone and other step 3 opioids, in particular morphine sulphate or hydromorphone. **Level 1a**
- A recent Cochrane systematic review (Schmidt-Hansen et al (2015)) assessing the efficacy of oxycodone for cancer pain demonstrated that oxycodone offers similar levels of pain relief and adverse events to other strong opioids including morphine, which is commonly considered the gold standard strong opioid (174). **Level 1a**

The available evidence demonstrates that the efficacy and tolerability of oxycodone is equivalent to that of morphine sulphate, hydromorphone and methadone, and these agents are all valid as first and subsequent choice opioids for the treatment of moderate to severe cancer pain. Methadone, due to its complex pharmacokinetic profile, should be used only under specialist guidance. **Level 1a**

**Hydromorphone**

Hydromorphone is a semi-synthetic derivative of morphine sulphate with similar pharmacokinetic and pharmacodynamic properties, though it is a more selective mu-opioid receptor agonist and thus has greater potency than morphine sulphate (148) (see section 2.2.5). It is metabolised in the liver to hydromorphone-3-glucuronide (H3G), which has no analgesic activity but does have neuro-excitatory properties (148). There is wide inter-individual variation in oral bioavailability (37-62%) (148).

Hydromorphone is available for oral use via immediate release and modified release preparations, and by injectable formulation. The lack of high strength oral formulations, particularly immediate release preparations, can pose problems for patients who are prescribed higher doses (2).

Pigni et al (2011) performed a systematic review examining the evidence supporting the use of hydromorphone for moderate to severe cancer pain (175).

- Few studies have been conducted on hydromorphone, despite its use over many years. Although this review included five RCTs, the studies in general had serious limitations in terms of missing data and bias, which precluded the performance of a meta-analysis. **Level 1b**
- Thirteen studies were identified evaluating the role of hydromorphone for cancer pain. Five RCTs were evaluated comparing hydromorphone to morphine sulphate and oxycodone, comprising 479 patients.

The available evidence demonstrates that the efficacy and tolerability of hydromorphone, morphine sulphate, oxycodone and methadone are equivalent. These agents are all valid choices as opioids for the treatment of moderate to severe cancer pain. Methadone should be used only under specialist guidance due to its complex pharmacokinetic profile (175). **Level 1b**

**Fentanyl**

Fentanyl is a strong mu-opioid receptor agonist. It is lipophilic, making it suitable for transdermal and transmucosal administration. Fentanyl is available for use transdermally (a patch), transmucosally (via buccal, sub-lingual or intra-nasal routes) or by injection (subcutaneous, intravenous or spinal routes) (148). The evidence for and use of transmucosal fentanyl for the relief of 'breakthrough pain' is discussed in section 2.3.2.2.

Sequestration occurs in body fats, including epidural fats and CNS white matter. By any route of administration, after systemic redistribution, fentanyl acts supraspinally. It is later metabolised to inactive norfentanyl via CYP3A4 in the liver (148).

Use of transdermal fentanyl preparations is associated with a lower occurrence of gastrointestinal side-effects and good patient compliance (161, 176).

Hadley at al (2013) performed a Cochrane systematic review of RCTs to determine the analgesic efficacy of transdermal fentanyl for cancer pain and assess adverse effects (177).

- Nine studies involving 1244 patients receiving transdermal fentanyl compared to placebo or active controls were identified. The studies were often small, used different study designs, and compared fentanyl with many different drugs.
- Most patients had pain that went from 'moderate or severe' before transdermal fentanyl to 'no worse than mild pain' when using transdermal fentanyl.
- Only 3 in 10 patients were constipated using transdermal fentanyl compared with 5 in 10 using oral morphine. The authors could not analyse the data in a meaningful way regarding harmful (adverse) events such as nausea, abdominal pain, gastrointestinal bleeding, and confusion, as these events may have been attributable to the underlying disease processes.
- They further concluded that the quality of evidence in these studies is severely limited (177).

**Level 1b**

More specifically, Tassarini et al (2011) performed a systematic review of the evidence for the use of transdermal fentanyl as a frontline approach to moderate to severe cancer pain, and found the level of evidence to be of low quality (161).

- In seven trials comparing transdermal opioids to oral morphine sulphate, no significant differences were found in the analgesic effect of the two treatments, and the main differences were extracted in the safety profile, and in patient preferences, although patient preferences were reported only for transdermal fentanyl.
- Only one study included used constipation as a primary outcome, but previous meta-analyses by the same authors suggested a lower rate of constipation with transdermal opioids (fentanyl and buprenorphine) compared to oral morphine sulphate. In addition, one study revealed a lower incidence of constipation, urinary retention, and laxative use with transdermal fentanyl compared to oral morphine sulphate (178).
- However, the heterogeneity of outcome measures and assessment of side-effects between trials mean that the risk / benefit ratio of transdermal opioids in favour of oral morphine sulphate remains uncertain, and at best only weakly favourable for transdermal fentanyl.
- The authors conclude that no definitive data exists to support an extensive use of transdermal opioids in all strong-opioid naïve patients with moderate to severe cancer pain, although they do remain a valid alternative when the oral route is not suitable (161).

**Level 2a**

**Alfentanil**

Alfentanil is a synthetic derivative of fentanyl, which is less lipophilic and has a more rapid onset of action and a shorter duration of action than fentanyl (148). It undergoes metabolism in the liver via CYP3A4 to inactive metabolites (148).

Alfentanil is available in injectable form and can be administered subcutaneously, intravenously and spinally. It is available in a more concentrated form than fentanyl and is thus a useful alternative in continuous infusions where high doses are required. Due to alfentanil's short duration of action, its use as an 'as required' opioid is best limited to breakthrough pain or for procedures (179). Its metabolites are not known to be active, and thus it is a preferred opioid in renal failure (see section 2.5.4). **Level 4**

Most research to date regarding the analgesic efficacy of alfentanil has been performed in the anaesthetic setting (148). Alfentanil has also been successfully used via continuous subcutaneous infusion in the burns and trauma settings (180). The evidence within the adult cancer pain setting relates mainly to the use of alfentanil in renal failure (see section 2.5.3.7 and 2.5.4). It has also been used sublingually for cancer-related breakthrough pain.

- No prospective trials could be identified for the purposes of these clinical guidelines regarding the efficacy of alfentanil for adult cancer pain outside the renal failure setting. Two case reports documented incidences of opioid withdrawal on rotation to alfentanil from hydromorphone (181) and oxycodone (172). King et al performed a systematic review of the evidence regarding opioids in renal impairment in 2011, and extracted data from two retrospective studies, of four and 41 patients respectively, in which patients were switched from other opioids to alfentanil due to renal impairment. Although the level of evidence is low, the authors concluded that alfentanil was a safe and efficacious opioid for use in renal failure, and recommended it as second line analgesia after fentanyl (179). **Level 4**
- Murtagh et al (2011) (182) and Reisfield et al (2007) (183) commented on the fast onset and short duration of action of alfentanil, giving it potential therapeutic potential for sublingual use as a fast acting agent, but unsuitable for 'PRN' use for breakthrough cancer pain.

**Buprenorphine**

Buprenorphine is a highly lipid-soluble opioid which demonstrates multimechanistic pharmacology, acting as a partial mu-opioid receptor agonist and a kappa- and delta-opioid receptor antagonist. It has low oral bioavailability (15%), is metabolised in the liver by CYP3A4 and is highly lipophilic (148). Buprenorphine is available in transdermal preparations for cancer pain management. Buprenorphine has been shown in in vivo studies to produce the same level of analgesic effect as other strong opioids including morphine and fentanyl (184).

Following a systematic literature review, Tassinari et al (2011) concluded that to date no definitive data exists to support the extensive use of transdermal opioids in all strong-opioid naïve patients with moderate to severe cancer pain and that the use of slow release oral preparations remains the preferred approach (161).

- The quality of evidence showing that transdermal buprenorphine was better than placebo or other oral/transdermal opioids was found to be very low, with an uncertain risk/benefit ratio. The recommendation given was of no net benefit to buprenorphine use. **Level 2a**
- Whilst the published data comparing transdermal fentanyl with transdermal buprenorphine is limited (176), the lower level of evidence supporting buprenorphine differentiates the two opioids in favour of transdermal fentanyl (161).

An updated systematic review in 2014 demonstrated that there is insufficient evidence to recommend the use of buprenorphine by the sublingual, intramuscular, or subcutaneous routes of administration for cancer pain. When administered transdermally, there is evidence that buprenorphine provides analgesia with possibly fewer side effects than other opioids, in particular regarding nausea. However, there is insufficient evidence to support the use of buprenorphine over any other strong opioid (185). **Level 1a**

**Methadone**

Methadone is a synthetic opioid with mixed properties; it is a mu-opioid receptor agonist, an NMDA receptor channel blocker and a pre-synaptic blocker of serotonin reuptake. It is absorbed well from all routes of administration, with 80% oral bioavailability. Methadone has a high volume of distribution due to its lipid solubility, and is extensively protein-bound. This results in a long and unpredictable plasma half-life, leading to potential problems with accumulation (148).

Due to these properties, leading to considerable inter-individual variation, the use of methadone for the treatment of cancer pain is advised only through the guidance of specialist palliative care professionals (2). Renal and hepatic impairment do not affect methadone clearance (see sections 2.4 and 2.5). **Level 2**

Methadone is available as an oral solution (standard solution or concentrate) and as an injectable formulation.

Cherny (2011) examined the role of oral methadone in cancer pain (186). Though the data was limited, largely derived from four studies (187-190), useful conclusions were drawn.

- A single study compared methadone to placebo for neuropathic pain and demonstrated evidence of analgesic effect at 20mg / day but not 10mg / day (186, 191).
- Four clinical studies evaluated the efficacy and safety of methadone in comparison to other oral or transdermal strong opioids (170, 186, 187, 189, 192). These studies were small, comprising 283 patients in total, and were of limited duration with variable methodological robustness. Consistent across all four studies, no evidence was found to suggest that methadone is a more effective analgesic than oral morphine sulphate or transdermal fentanyl, or that methadone is associated with fewer side-effects than oral morphine sulphate or transdermal fentanyl (186). **Level 1b**

However, the success of treatment with methadone may be compromised by inappropriate dose selection or lack of close monitoring during initiation of therapy (186).

As stated previously, the available evidence demonstrates that the efficacy and tolerability of methadone, morphine sulphate, oxycodone, and hydromorphone are equivalent, and these agents are all valid choices as first and subsequent use opioids for the management of moderate to severe cancer pain. Methadone however, due to its complex pharmacokinetic profile, should be used only under specialist guidance (193).

**Best Practice Point: Pharmacoeconomics**
Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

**Recommendation 8 Choice of opioid**
**The following are responsible for implementation of recommendation 8:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>The available evidence demonstrates that the efficacy and tolerability of morphine sulphate, oxycodone, hydromorphone and methadone are equivalent, and these agents are all valid choices as first and subsequent choice opioids for moderate to severe cancer pain.<br><br>Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients; they may be associated with less constipation and good patient compliance, but their pharmacokinetic and dynamic characteristics present challenges. | |
| **Key recommendations** | |
| **B** | **8.1** Oral morphine sulphate, hydromorphone and oxycodone may be used as first line treatment in the management of moderate to severe cancer pain. |
| **B** | **8.2** Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients. |
| **D** | **8.3** Methadone may be used for the treatment of moderate or severe cancer pain. |
| **D** | **8.4** Methadone use is only advised through the guidance of specialist palliative care professionals. |

### *2.3.2 Route of administration of opioid*

Oral opioids have been recommended as the mainstay of cancer pain management (2, 52, 65, 73, 121, 139). If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes.

- Radbruch et al (2011) performed a systematic literature review on the use of alternative routes for opioid administration and found 18 relevant studies (194).
- The best evidence (from one systematic review and three RCTs) was found for subcutaneous administration of morphine sulphate or other opioids (194).

**Level 1b**

There was less evidence available for other routes of administration. However, the review found no significant difference in efficacy or side-effects between the alternative application routes investigated (194). Thus, subcutaneous, intravenous, rectal and transdermal routes are all useful alternatives for opioid administration, where oral treatment is not possible.

**Recommendation 9 Route of administration of opioid**
**The following are responsible for implementation of recommendation 9:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>The oral route should be used for administration of opioids, if practical and feasible. Alternative routes are found to be as effective from an efficacy and side effect profile perspective. | |
| **Key recommendation** | |
| **A** | The oral route should be used for administration of opioids, if practical and feasible. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes. |

### *2.3.2.1 Oral administration of opioids*

Morphine sulphate, oxycodone and hydromorphone can be administered as immediate (IR) or modified release (MR) (sometimes called 'sustained release' or SR). Peak plasma concentrations normally occur within one hour of administration of an immediate release morphine sulphate preparation, with reasonably rapid onset of analgesia which then lasts for about 4 hours. In contrast, modified release formulations produce a delayed peak plasma concentration after 2-6 hours and analgesia lasts for 12 to 24 hours (195).

In terms of analgesic efficacy, there is no difference between four-hourly, twelve hourly and twenty four hourly dosing of morphine sulphate (196, 197) or oxycodone preparations (198). **Level 1b**

**Recommendation 10 Oral opioid dose schedule**
**The following are responsible for implementation of recommendation 10:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>When considering dosing schedule, there is no difference between the available oral opioid preparations in terms of analgesic efficacy, once they are correctly administered. | |
| **Key recommendation** | |
| **D** | As there is no difference between the available oral opioid preparations in terms of analgesic efficacy, oral opioid scheduling should be based on patient preference and ease of compliance. |

**Opioid initiation and titration**
Traditionally, when starting morphine sulphate for cancer pain, the recommendation has been to use immediate release (IR) oral morphine sulphate every 4 hours, with the same dose for breakthrough pain. This recommendation is based on the WHO analgesic pain ladder framework (121) and formed part of the 2001 EAPC cancer pain guidelines (139). Recently this concept has been challenged.

- Klepstad et al (2011) (199) performed a systematic review of the evidence regarding initiation of opioid treatment in patients with moderate to severe cancer pain, not previously on opioid therapy. The evidence was found to be limited. Fifteen relevant articles were identified, of which two were RCTs and thirteen were descriptive studies. The authors conclude that opioid treatment could be adequately and safely started with a number of therapeutic approaches, including titration with immediate release morphine sulphate or titration with IV morphine sulphate (199). Where fast onset of pain relief is crucial, the intravenous route may be the more efficient choice (200). **Level 2a**
- It is argued that using modified release morphine sulphate during titration spares the patient a multiple-dosing schedule which can be perceived as cumbersome and possibly as 'overmedication' by patients (reducing compliance) (199). Given the present available knowledge, there is evidence that oral opioid titration can be performed with oral immediate release preparations or oral modified release preparations.

The starting dose of analgesia will depend on the severity of pain, the side-effects of present or prior analgesia, and the total amount of analgesia required by the patient previously. Given the present available knowledge, descriptive studies demonstrate that starting with oral morphine sulphate up to and including a dose of 30mg/24hr in opioid naïve patients, or up to and including a dose of 60mg/24hr in those patients titrating from step two opioids, is safe and efficient (199). For patients converted from another step three opioid, please refer to section 2.3.5 on equianalgesic dosages to guide management.

**Table 6** Titration using immediate release oral preparations

**Titration Using Immediate Release Oral Preparations**
(Using oral morphine sulphate as an example)

- Use immediate release morphine sulphate, given every 4 hours, and the same dose for breakthrough pain. This rescue dose may be given as often as required and the total daily dose of the morphine sulphate should be reviewed daily.
- If pain returns consistently before the next regular dose is due, the regular dose should be increased. Patients stabilised on regular oral morphine sulphate require continued access to a rescue dose to treat breakthrough pain.
- When a patient's pain has been controlled with immediate release morphine sulphate, the 24 hour dose can be converted into modified 12 hour release preparation.

For example*
- A patient is taking immediate release morphine sulphate 10mg every four hours.
- This means that they are taking 60mg of morphine sulphate in 24 hours.
- The patient can be commenced on morphine sulphate 30mg twice daily, if using a 12 hourly preparation

**** This conversion is by way of example. Individualised titration is always recommended and is dependent on clinical assessment.***

**Table 7** Titration using modified release oral preparations

| **Titration Using Modified Release Oral Preparations**<br>(using oral morphine sulphate as an example) |
|---|
| • Use a modified release preparation, such as a 12 hourly morphine sulphate preparation (e.g. MST®) prescribed twice daily. Co-prescribe an immediate release oral morphine sulphate preparation, to be taken as often as required as a breakthrough dose. See section 2.3.2.2 on appropriate dosage for breakthrough pain prescribing.<br>• After 24 hours, assess the effectiveness of the regimen based on clinical assessment of the patient and calculation of the number of breakthrough analgesic doses required. Titrate the modified release formulation accordingly<br><br>For example*<br>• A patient is taking modified release oral morphine sulphate 15mg bd (e.g. MST 15mg bd) and has required 4 breakthrough doses of immediate release oral morphine sulphate 5mg<br>• This means the patient has taken 50mg of morphine sulphate in 24 hours<br>• The patient's modified release oral morphine sulphate should be titrated to 25mg twice daily (also adjust breakthrough dose)<br>• A further assessment of pain and potential dose titration is made after a further 24 hours, and so forth. |

**** This conversion is by way of example. Individualised titration is always recommended and is dependent on clinical assessment.***

Patients stabilised on regular oral morphine sulphate require continued access to a rescue dose to treat breakthrough pain (see section 2.3.2.2 on breakthrough pain).

**Recommendation 11 Oral opioid treatment**
**The following are responsible for implementation of recommendation 11:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding**<br>Opioid treatment can be adequately and safely started with a number of therapeutic approaches. | |
|---|---|
| **Key recommendation** | |
| **C** | Oral opioid titration can be adequately and safely commenced and titrated using either oral immediate release preparations, or modified release preparations. |

### *2.3.2.2 Breakthrough pain*

Breakthrough pain is a transitory exacerbation of pain experienced by the patient with stable and adequately controlled baseline (background) pain. The use of a pharmacological 'rescue' or 'breakthrough' dose of analgesia is widely accepted as the management of breakthrough pain (46). There has been lack of consensus in the literature on a formal definition, leading to difficulties when comparing studies and recommending management strategies (201). Breakthrough pain is recognised as a transient increase in pain intensity over background pain. It is usually related to background pain and is typically of rapid onset, severe in intensity, and generally

self-limiting with an average duration of 30 minutes (202). A large observational study found breakthrough cancer pain to be an extremely heterogenous condition, with wide variation in median time to peak intensity and response to treatment (203). It is a common and distinct component of cancer pain, which can have a negative impact on both the patient and carers' quality of life. A systematic review of observational studies found that the prevalence of breakthrough cancer pain ranges from 39% in cancer outpatients, to 80% in hospice inpatients (204).

**Level 2b**

**Level 2a**

The presence of breakthrough pain is generally a marker of a more severe pain syndrome and is associated with both pain-related functional impairment and psychological distress (205). It is a poor prognostic indicator (206) and has been associated with a decreased functional status, anxiety and depression and longer stays in hospital (205, 207).

**Level 2b**

Payne (2007) describes three types of breakthrough pain (208):

- Incident pain: This is pain that is associated with movement (voluntary or involuntary)
- Idiopathic or spontaneous pain: This has no identifiable cause and tends to last longer than incident pain
- End of dose failure: This occurs prior to the next scheduled dose of analgesia and is often not regarded as true breakthrough pain.

It is important to discern the pattern of the breakthrough pain, as the management may alter accordingly. For example, end of dose failure may be treated by upward titration of the background analgesia, whereas incident pain may be treated by an anticipatory dose of breakthrough analgesia.

The management of breakthrough pain involves the following approaches (209):

1. Optimise background 'around-the-clock' analgesia
2. Non-pharmacological management:
   - Implementing primary therapies: Surgery, radiotherapy and chemotherapy
   - Non-pharmacological therapies: These include avoidance of factors known to precipitate pain, engagement in physical therapy, education about physical limitations and exacerbating factors, and patient counselling to reduce anxiety (210).
3. Pharmacological management:
   Patients require continued access to a rescue dose to treat 'breakthrough' pain, as enshrined in the WHO cancer pain framework (121). It is important to tailor management for the type of breakthrough pain being experienced.
   - Pain episodes of **uncontrolled background pain** should be treated with additional doses of normal release oral formulations
   - **Incident pain:** Treating incident pain involves the pre-emptive use of a short-acting opioid 30 minutes before the precipitating activity (210)
   - **Idiopathic/ spontaneous:** The peak intensity for this type of pain can occur in 3-5 minutes and episodes usually last for under 30 minutes. Therefore, analgesics with a delayed onset are not helpful for this type of pain
   - **End of dose failure:** For end of dose failure, there is a need to alter the around the clock medication to increase the dose or shorten the dosing interval (210, 211).

**Treatment of breakthrough pain**

The usual approach to the management of breakthrough pain has been to use supplemental doses of oral immediate release opioids ('rescue' medication), based on the patient's background analgesia, given before or soon after breakthrough pain has started. Traditionally, two approaches were favoured:

- Use of the equivalent four-hourly dose for rescue medication, with subsequent increases or decreases according to clinical effect (this is one sixth of the daily dose) (139)
- Use of short-acting opioid rescue doses of between 10%–20% of the 24 hour oral dose (mg) every 1 hour, as needed (52).

**Level 5**

Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations. More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed (211).

**Level 1b**

**Transmucosal fentanyl preparations**

In recent years, a number of transmucosal preparations have been developed specifically to target breakthrough pain.

In order to evaluate the efficacy of transmucosal fentanyl, Zepetella et al performed a Cochrane systematic review in 2013 (212). 15 studies were included with a total of 1699 participants. 7 different preparations examined – 5 oral (buccal), 2 nasal of transmucosal fentanyl were included: 8 studies which compared transmucosal fentanyl citrate and placebo; 4 studies which compared transmucosal fentanyl citrate and another opioid; 1 study which compared 2 doses of the same formulation of fentanyl; and 2 randomised titration studies. The systematic review concluded that both buccal and nasal fentanyl formulations are effective treatments for breakthrough cancer pain when compared to placebo or oral morphine sulphate. However, more research, including head to head comparisons of different formulations of fentanyl, are needed (212).

**Level 1a**

- Transmucosal fentanyl products should only be used in opioid-tolerant patients (52) (see manufacturer's recommendations).
- The buccal, sublingual and nasal routes can be safely used to provide analgesia, with an onset of action within 10 minutes of administration. Comparison with parenteral opioids showed superiority for the parenteral route at 15 minutes, but both routes were equally effective at 30 minutes (213).

Most studies examining the efficacy of transmucosal fentanyl found no correlation between the background opioid dose and the transmucosal or oral rescue doses (139, 201). As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is recommended (201). There is a lack of strong evidence to favour one product over another, and choice of drug is likely to come down to drug availability physician familiarity, and patient characteristics (214). Further studies are required in this area, in particular head to head studies comparing different formulations using validated assessment tools.

**Level 1b**

**Recommendation 12 Breakthrough pain**
**The following are responsible for implementation of recommendation 12:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Breakthrough pain is common and can have a negative impact on quality of life.<br><br>Patients should have breakthrough medication prescribed and this dose should be titrated according to the individual and to the type of breakthrough pain being experienced.<br><br>There is a lack of strong evidence to favour one product over another, and choice of drug is likely to come down to drug availability physician familiarity, and patient characteristics. Further studies are required in this area, in particular head to head studies comparing different forumulations using validated assessment tools. | |
| **Key recommendation** | |
| **A** | Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations.<br><br>More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed.<br><br>As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is recommended. |

### *2.3.2.3 Alternative routes of administration of opioids*

**Parenteral opioids**
Radbruch et al (2011) reviewed the evidence for the use of subcutaneous and intravenous routes of opioid administration (194).

The best evidence base was available for the subcutaneous route, including a systematic review and three randomised controlled trials.

- Eleven studies comprising 466 patients were found which compared the subcutaneous route with different application routes. Four studies compared subcutaneous with intravenous applications (in three studies with morphine sulphate, and in one with hydromorphone). No differences in efficacy or safety were reported. One study compared rectal and subcutaneous morphine sulphate use, the other six studies used sequential switches from intravenous to subcutaneous application, or from transdermal to subcutaneous use. All studies reported good analgesic efficacy with subcutaneous use.
- A further twenty four studies including 1102 patients were identified that reported on the subcutaneous use of opioids (including morphine sulphate, oxycodone, hydromorphone, fentanyl and methadone).
- Local toxicity at subcutaneous needle insertion sites was infrequent. Systemic side-effects were comparable between intravenous and subcutaneous route, and were as expected with opioid treatment (most often constipation, nausea and drowsiness).

**Level 1b**

**Intravenous administration**

- Twelve studies comprising 296 patients were identified comparing intravenous with other routes of administration. Seven of these compared intravenous with subcutaneous application, including two RCTs. No difference was reported between these two routes in terms of efficacy or tolerability, though onset of pain relief was faster using the intravenous route. The other studies compared the intravenous route with rectal and transdermal routes. **Level 1b**
- A further nine studies comprising 549 patients reported on intravenous use of morphine sulphate, hydromorphone, methadone and oxycodone. Efficacy and tolerability were similar (194).

Radbruch et al (2011) conclude that both the subcutaneous and intravenous routes are feasible, effective and safe (194). The intravenous route may be preferable where rapid titration of analgesia in cases of severe uncontrolled pain is required. However, due to the lower risk of complications, the subcutaneous route is generally preferred (22, 194). **Level 1b**

**Intravenous infusions of morphine sulphate may be preferred to subcutaneous infusions in patients:**

- Who already have an indwelling intravenous line or port system
- With generalised oedema
- Who develop erythema, soreness or sterile abscesses with subcutaneous administration
- With coagulation disorders
- With poor peripheral circulation.

**Oral to parenteral conversion**

Radbruch et al (2011) report that, in studies comparing intravenous and subcutaneous application of the same opioid, analgesic effective doses were similar for both routes (194). **Level 1b**

Conversion factors have been described in some studies, but mostly only calculated from small numbers of patients and often with a wide variation between studies (194). A conversion ratio for oral: intravenous morphine sulphate between 2:1 and 3:1 is supported by some evidence; Takahashi et al (2003) reported an oral to intravenous morphine sulphate conversion of 2.9 : 1 for those on chronic morphine sulphate treatment (215) and this figure has been followed in the 2012 EAPC pain recommendations (22). The ratio is similar for oral to subcutaneous morphine sulphate. Inter-individual variability between patients should be noted. Please see section 2.2.5 on opioid equivalencies for further detail. **Level 3**

**Use of continuous infusions**

Continuous subcutaneous infusion of opioids is simple to administer and as effective as continuous intravenous infusion (2, 194). Syringe driver infusion pumps may be used to avoid the need for regular bolus injections for those on regular opioids, where the oral route is no longer appropriate. **Level 1b**

Many opioids can be used alone or in combination with other medications in a syringe driver infusion. However, the small volumes of infusate used in a syringe driver can mean that drug concentrations used are high, and when used in combination with other medications this may precipitate drug incompatibilities. It is therefore important to ensure that healthcare staff that are using syringe drivers are familiar with them, and that advice regarding the compatibility of the drugs is freely available. Information can be obtained from sources such as the Palliative Care Medicines Information Service, available from palliativemedsinfo@olh.ie.

**Indications for the use of continuous infusion include:**
- Intractable vomiting
- Severe dysphagia
- Patient too weak to swallow oral medication
- Decreased level of consciousness
- Poor gastrointestinal absorption
- Poor patient compliance.

**Recommendation 13 Parenteral routes of opioid administration**
**The following are responsible for implementation of recommendation 13:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Subcutaneous and intravenous routes of administration are feasible, effective and safe for the administration of opioid medication in cancer pain. | |
| **Key recommendations** | |
| **A** | **13.1** Subcutaneous and intravenous routes may be used where the oral route is not feasible. |
| **C** | **13.2** The average relative potency ratio of oral morphine sulphate to subcutaneous or intravenous morphine sulphate is between 2:1 and 3:1, with variability between patients. |

#### *2.3.2.3.1 Transdermal opioids*

Both fentanyl and buprenorphine are strong opioids that can be administered via transdermal preparations (216).

- Radbruch et al (2011) evaluated seven studies comparing transdermal with alternative routes of administration. It was noted to be difficult to differentiate between the effects of the opioid switch (e.g. from oral morphine sulphate to transdermal fentanyl) and those resulting from a change of route of administration. Those studies where the same drug was used but administered through different routes support the finding that efficacy and tolerability are similar between the transdermal route and other routes of opioid administration (194). **Level 2b**
- Local symptoms at the application sites of transdermal opioids are reported, such as localised erythema (3 to 27.3%) and pruritis (3.7 to 24.8%) (194). Transdermal absorption may be impaired in cachectic patients (217). **Level 2b**

**Transdermal fentanyl**
Transdermal fentanyl is effective and well tolerated for the treatment of chronic pain caused by malignant and non-malignant conditions, when administered according to the manufacturer's recommendations. Transdermal fentanyl is a useful analgesic for cancer patients who have stable pain and who are unable to swallow or have gastrointestinal problems. The 72-hour transdermal fentanyl patch forms a depot within the upper skin layers before entering the microcirculation. Therapeutic blood levels are attained 12-16 hours after patch application and decrease slowly with a half-life of 16-22 hours following removal. Patients with chronic pain should be titrated to adequate relief with short-acting oral or parenteral opioids prior to the initiation of transdermal fentanyl, in order to prevent exacerbations of pain or opioid-related

adverse effects (218). Transdermal fentanyl can then be initiated based on the 24-hour opioid requirement, once adequate analgesia has been achieved.

Fentanyl is evenly distributed throughout a drug-in-adhesive matrix, and the release of fentanyl is controlled by the physical characteristics of the matrix. Therefore, it is possible to cut patches with a matrix formulation in half. The administration of half a patch is unlicensed, although the practice is common in clinical settings. The second half of the patch cannot be kept for future use and it must be disposed of immediately and appropriately.

The most accepted approach to commencing transdermal fentanyl is as follows (216):

- Calculate the previous 24-hour analgesic requirements
- Convert this amount to the equianalgesic oral morphine sulphate dose
- Determine the corresponding transdermal fentanyl dose (see section 2.5)
- Initiate treatment using this recommended dose and titrate dosage upwards (no more frequently than every 3 days) until analgesic efficacy is attained.

There have been several case reports in the literature documenting withdrawal syndromes associated with conversion from oral opioids to transdermal fentanyl (219, 220). This is due to a 'lag phase' after commencing transdermal fentanyl before which therapeutic concentrations are achieved. This may be as long as 12-18 hours after the initial patch is applied. The SIGN guidelines outline an approach to minimise the risk of this as follows (2):

When converting from an oral strong opioid to transdermal fentanyl (72 hour patch):

- if taking 4 hourly oral opioid, continue for 12 hours after applying transdermal patch
- if taking 12 hourly oral opioid, give the last dose when the first transdermal patch is applied
- for a patient receiving opioids via CSCI, apply the patch and continue the syringe driver for 6 hours after application.

Medication for breakthrough pain should also be prescribed (see section 2.3.2.2).

**Transdermal buprenorphine**

Buprenorphine is also available in a patch preparation. It is available as 'BuTrans®' 7-day patch and a 72-96 hour 'Transtec®' patch. Both use a matrix delivery system.
When titrating a buprenorphine patch, much like the fentanyl patch, there is a lag phase after the initial application. It can take 12-24 hours for the buprenorphine patch to reach minimal effective concentration.

**Recommendation 14 Transdermal opioids**
**The following are responsible for implementation of recommendation 14:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Transdermal fentanyl and buprenorphine patches are valid alternative delivery systems for patients with **stable** pain who require regular opioid analgesia. | |
| **Key recommendations** | |
| **D** | Use of the transdermal route is suitable for patients who have **stable** pain. Patients should be titrated to adequate pain relief with oral or parenteral opioid pain medications prior to the initiation of transdermal patches. Medication for breakthrough pain should also be prescribed. |

**Transmucosal opioids**
Opioid administration via the buccal, sublingual or nasal mucosa as an alternative route of administration was examined systematic review by Radbruch et al (2011) (194). Whilst morphine sulphate's absorption is unpredictable by these routes, highly lipophilic drugs such as fentanyl and buprenorphine can be rapidly absorbed and many new therapeutic systems for transmucosal opioid delivery have been developed in recent years. However, these new systems are indicated only for the treatment of breakthrough pain, and their role in the treatment of continuous pain is limited. Rectal administration of opioids such as morphine sulphate or methadone is not commonly practiced in Ireland, but can be used effectively. Similar efficacy and tolerability with subcutaneous or intravenous application has been described (194). **Level 1b**

**Spinal opioids**
Since endogenous opioids and opioid receptors were first isolated in the central nervous system in the 1970s, attempts have been made to optimise opioid therapy by central delivery of opioids (221). In those patients whose pain is refractory to systemic opioid treatments, there may be specific reasons that a patient may benefit from neuraxial (epidural, intrathecal and intracerebroventricular) administration of opioids, such as (222):

- Unacceptable side-effects despite successful analgesia with systemic opioids
- Unsuccessful analgesia despite escalating doses and use of sequential systemic opioids
- Intolerable neuropathic pain which may be amenable to spinal adjuvants
- Incident pain which may benefit from numbness (local anaesthetic).

Intrathecal opioids act by binding to mu and kappa receptors in the substantia gelatinosa of the spinal cord. This is achieved to a lesser extent with epidural opioids which exert both a systemic effect (10%) and an intrathecal effect (90%). There is growing evidence favouring the intrathecal route of administration due to better long term pain outcomes, the lower dose required, the fewer systemic side-effects and the lower complication rates (223).

Kurita et al (2011) performed a systematic review to analyse the analgesic efficacy and side-effects of spinal opioids in adult cancer patients previously treated with systemic opioids (221).

Few studies of high quality design were found, and many had methodological limitations that reduced their quality of evidence to very low. The authors conclude that neuraxial opioid therapy is only indicated where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia (221).

**Level 2a**

Consideration should be given to absolute and relative contraindications of spinal techniques. The mainstay drug for long-term spinal use has been morphine sulphate; although lacking in randomised trials, its use is supported by a relatively large published literature. Beyond this, strategies include the combination of morphine sulphate with local anaesthetic (such as bupivicaine); combination with clonidine (an alpha-2 adrenergic agonist); or the use of an alternative opioid such as hydromorphone or fentanyl (2, 221). The empirical data supporting these approaches is very limited and there is no data to support the use of one approach over another. The use of spinal routes of administration of analgesia requires specialist input.

**Recommendation 15 Spinal opioids**
**The following are responsible for implementation of recommendation 15:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. The responsible physician caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Spinal opioid therapy may be effective for treating cancer pain where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia. | |
| **Key recommendations** | |
| **D** | Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made.<br><br>Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. |

**Topical (transcutaneous) opioids**
The management of painful skin and mucosal lesions presents a therapeutic challenge. The effective use of systemic opioids for such conditions can be complicated by unpredictable bioavailability of the drug within the wound microenvironment, largely due to impaired circulation (224). These limitations, and the identification of peripheral opioid receptors, have triggered an interest in exploring alternative routes of analgesia, such as topical application.

LeBon et al (2009) performed an extensive systematic review in order to appraise the evidence for such an approach.

- Nineteen articles were included in the review, comprising six RCTs and thirteen case reports. Whilst there is support for the use of topical opioids, due to the wide heterogeneity of the studies the authors were unable to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, methods of titration, carrier agent or most suitable wounds for this treatment (224).

**Level 1b**

**Recommendation 16 Topical opioids**
**The following are responsible for implementation of recommendation 16:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>There is limited evidence to support the use of topical opioids in the management of painful malignant skin and mucosal lesions. | |
| **Key recommendation** | |
| **D** | Whilst there is support for the use of topical opioids, there is insufficient evidence to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, method of titration, carrier agent or most suitable wounds for this treatment. |

### *2.3.3 Opioid side-effects and toxicity*

Opioid use can be associated with many side-effects (225). Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria, a substantial minority of patients treated with oral morphine sulphate (10% to 30%) do not have a successful outcome because of excessive adverse effects, inadequate analgesia, or a combination of both excessive adverse effects along with inadequate analgesia (136).

Opioid reduction or rotation should be considered as a useful strategy to manage opioid side-effects (22, 226) and is further discussed in section 2.3.4. **Level 2a**

#### *2.3.3.1 Opioid side-effects*

**Dry mouth**
Anderson et al (2004) reported that dry mouth is the most common adverse effect of opioids (227). Concomitantly, many patients may be on other medications that have anticholinergic properties, worsening this symptom. All patients should be educated on the need for, and methods to achieve, good oral hygiene (73). Frequent administration of oral saliva replacement gels may be helpful. **Level 5**

**Nausea and vomiting**
Up to 40% of cancer patients with no prior emesis may experience opioid-induced nausea and/or vomiting (228). The pathophysiology of opioid-induced nausea relates to constipation, gastroparesis, stimulation of the chemoreceptor trigger zone and sensitisation of the labyrinth, all of which trigger the signaling cascade involving the vomiting centre.

- Laugsand et al (2011) systematically reviewed fifty-five studies providing data on 5741 patients (229). Eighteen studies were identified as primarily addressing symptomatic treatment of nausea and vomiting in cancer patient cohorts, however the overall quality of evidence was poor due to significant heterogeneity between the studies, and lack of information in study design and outcomes. **Level 1b**
- Thus, the authors formulated weak recommendations only; that current evidence is too limited to provide evidence-based recommendations for the use of anti-emetics in opioid-induced nausea/vomiting in cancer patients; that in those patients receiving an opioid, symptoms may be reduced by changing the opioid or the route of administration of the opioid. **Level 1b**

- Recommendations for the choice of anti-emetics in this population must therefore still be based upon knowledge of aetiologic mechanisms and expert opinion.
- Furthermore, Laugsand et al found that it is not possible to prioritise between symptomatic treatment with anti-emetics and adjustments of the opioid treatment in the management of opioid-induced nausea and vomiting (229). **Level 1b**

Opioid induced nausea and vomiting mostly occurs on initiation of treatment and tends to subside within 3-5 days (44). Therefore, it is important to have an anti-emetic available for the patient as needed, especially when commencing opioid treatment.

**Constipation**

Opioids slow peristalsis, promote fluid reabsorption and inhibit fluid secretion into the intestinal lumen. The combination of these factors often results in constipation. Chronic constipation has been observed in 20-70% of patients treated for chronic cancer pain (136). Whilst general principles of prevention should be followed, pharmacological treatment is often necessary (230). More recently, peripheral opioid antagonists such as methylnaltrexone have been introduced for the treatment of opioid-induced constipation (e.g. Relistor®).

- Sykes et al (1996) (231) conducted a volunteer model study for the comparison of laxatives in opioid-related constipation. This study found that a combination of stimulant and softening laxatives was most likely to maintain normal bowel function at the lowest dose and least adverse effects; this recommendation was endorsed by the 2008 EAPC clinical practice recommendations (230). There is no evidence to favour the choice of one particular laxative over another. **Level 5**
- Candy et al (2011) updated the 2006 Cochrane review on the management of constipation in palliative care patients (232). Seven RCT studies were included, comprising 616 participants; all studies had methodological limitations.
  - The evidence was inconclusive in the four RCTs comparing different laxatives, and there remains no evidence to favour the choice of one laxative over another. **Level 1b**
  - Three RCTs examined the use of subcutaneous methylnaltrexone where conventional laxatives have failed. In combined analysis (287 patients), significant induced laxation was found at four hours, in comparison with placebo. No difference in the proportion experiencing side-effects was shown, although those on methylnaltrexone experienced more flatulence and dizziness. No evidence of opioid withdrawal was found. One study reported severe adverse events (commonly abdominal pain). The authors conclude that whilst subcutaneous methylnaltrexone was found to be effective in inducing laxation in palliative care patients with opioid-induced constipation where conventional laxatives have failed, the safety of this product is not yet fully evaluated (232). **Level 1a**

The use of subcutaneous methylnaltrexone should be restricted to those patients whose treatment is resistant to traditional laxatives (22, 230, 232). Combination medications of oral opioids with oral naloxone (e.g. Targin®) have been introduced as a strategy for reducing the incidence of opioid-induced constipation. **Level 5**
Oxycodone combined with Naloxone (Targin®) has been shown to be effective and safe in doses up to 120mg per day and be equianalgesic to oxycodone alone and result in patients using 20% less rescue laxative medication, however studies in cancer patients are limited as are comparisons with strong opioids other than oxycodone (233, 234). **Level 1b**

- Guidance on the management of constipation in cancer is available in the National Clinical Guideline No 10 *Management of Constipation in Adult Patients Receiving Palliative Care*.

**Respiratory depression**

One of the most serious complications of opioid therapy is potential respiratory depression. It rarely occurs in cancer pain management. It is more likely to occur at initiation of therapy, at dose titration, or after opioid switching, especially to methadone (225) (see section 2.3.3.3). **Level 5**

**Recommendation 17 Opioid side-effects**

**The following are responsible for implementation of recommendation 17:**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Opioid therapy can be associated with many side-effects. | |
| **Key recommendations** | |
| **D** | **17.1** It is important to anticipate and monitor patients for opioid side-effects and manage these at the earliest opportunity to prevent unnecessary morbidity. |
| **D** | **17.2** The current evidence is too limited to provide evidence-based recommendations for the use of anti-emetics in opioid-induced nausea/vomiting in cancer patients. Choice is therefore based on knowledge of aetiology and expert opinion. |
| **D** | **17.3** In the management of opioid-induced constipation, the combination of a softener and stimulant laxative is generally recommended, and the choice of laxatives should be made on an individual basis[2]. |
| **D** | **17.4** The use of peripheral opioid receptor antagonists (methylnaltrexone) should be restricted to those patients whose treatment is resistant to traditional laxatives. |

**Neuropsychological side-effects (235)**

In a prospective study of 40 patients receiving intermittent narcotic analgesics, Bruera et al (1989) reported that defects in formal cognitive testing occur, particularly on initiation of opioid therapy and in association with dose increments of at least 30%. Cognitive impairment was reported to disappear within one week of the dose increment (236). The actual patient distress associated with mild cognitive deficits is uncertain, however sedation may be a prelude to the development of delirium and more florid neurotoxicity (237). Sedation and respiratory depression tend to occur on a continuum. Therefore it is important to monitor patients exhibiting sedation as a result of opioid therapy. This is most likely to occur on initiation of opioids or after dose titration (237). **Level 2b**

Stone et al (2011) performed a systematic review of the evidence for the management of opioid-induced central side-effects, such as sedation, cognitive dysfunction, sleep disturbance, myoclonus, hyperalgesia and delirium (235).

- Twenty-six studies were reviewed; the data was found to be of low quality and thus the recommendations made are weak. The review did **not** examine studies where opioid side-effects were managed by switching or substituting opioids, by introducing co-analgesics, or by reducing the dose of the prescribed opioid (see section 2.2.4 for role of opioid rotation). **Level 1b**
- Methylphenidate may have a role for the management of opioid-induced sedation in patients for whom opioid dose reduction or rotation is impractical or inappropriate (235). **Level 1b**

- Given the present available knowledge, no recommendation can be made for or against the use of specific drugs for the relief of opioid-induced myoclonus, sleep disturbance or hyperalgesia.

**Delirium**

Delirium is a neuropsychiatric disorder characterized by an acute onset, a fluctuating course, disorganized thinking and altered levels of consciousness. It is associated with defined underlying causes such as general medical conditions, medication or substance toxicity or withdrawal, or a combination of factors (238).

- Lawlor et al (2000) performed a prospective study of the occurrence, causes, and outcome of delirium in 113 patients with advanced cancer (239). This study found that delirium is a frequent, multi-factorial complication in advanced cancer. Despite its terminal presentation in most patients, delirium is reversible in approximately 50% of episodes. Delirium precipitated by opioids and other psychoactive medications, and dehydration, is frequently reversible with change of opioid or dose reduction, discontinuation of unnecessary psychoactive medication, or hydration, respectively (239). **Level 2b**

The treatment of delirium firstly involves the search for an identifiable underlying cause and the treatment of this cause (for example sepsis, hypercalcaemia, uraemia). Although no studies have assessed the use of most commonly used interventions such as haloperidol in the management of opioid-induced cognitive impairment, a large body of literature attests to its effectiveness for the treatment of agitated delirium in other patient groups, or in delirium caused by other factors (235). Thus, haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances (235, 239).

Other side-effects of opioids include pruritis, sweating, micturition disturbance and vertigo (225).

2 See National Clinical Guideline 10. Management of Constipation in Adults Patients Receiving Palliative Care

**Recommendation 18 Neuropsychological opioid side-effects**
**The following are responsible for implementation of recommendation 18:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Opioids may cause neuropsychological side-effects, such as sedation, cognitive dysfunction, sleep disturbance, myoclonus, hyperalgesia and delirium. Delirium is a frequent, multi-factorial complication in advanced cancer. Delirium precipitated by opioids is frequently reversible. | |
| **Key recommendations** | |
| **B** | **18.1** Opioid reduction or rotation should be considered as a useful strategy to manage opioid side-effects. |
| **D** | **18.2** Given the present available knowledge, no recommendation can be made for or against the use of specific drugs for the relief of opioid-induced myoclonus, sleep disturbance or hyperalgesia. |
| **B** | **18.3** The treatment of delirium firstly involves the search for an identifiable underlying cause and the treatment of this cause. |
| **D** | **18.4** Haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances. Opioid reduction or rotation should be considered. |

### *2.3.3.2 Risk of opioid dependence in cancer pain treatment*

It is known that cancer pain is often undertreated. De Andrea at al (2008) performed a systematic review on the prevalence of under-treatment in cancer pain, which included 26 studies published from 1994 to 2007 (240). They found that approximately 50% of patients are undertreated; one reason for this is physician reluctance to prescribe opioids at adequate dosages due to concerns linked to potential adverse effects, including fatal opioid overdose, development of tolerance and dependence syndrome, harmful use of opioid and diversion (240). According to the DSM (241), dependence is a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues to use the substance despite significant substance-related problems.

**Level 2a**

Minozzi et al (2012) performed a systematic review with the objective of assessing the incidence or prevalence of dependence syndrome in adults with and without previous history of substance abuse following treatment with opioid analgesics for pain relief (242).

- Among almost 2000 titles and abstracts scrutinised, very few assessed or reported data on development of dependence. In total, data was extracted from 17 studies, involving a total of 88 235 participants. The studies included three systematic reviews, one RCT, eight cross-sectional studies and four uncontrolled case series. Included are patients with cancer and non-cancer pain, both acute and chronic.
- Incidence ranged from 0 to 24% (median 0.5%); prevalence ranged from 0 to 31% (median 4.5%).
- In terms of cancer patients, it was not possible to retrieve information on incidence of dependence, as only two studies with a total of 118 patients reported data; in

**Level 2a**

one, none of the subjects developed dependence, while no conclusions could be drawn from the other, as it did not disaggregate the data relating to cancer pain from the non-cancer pain data, and cancer pain patients accounted for only 7% of the total sample.

- Furthermore it was not possible to determine directly the specific risk of dependence among patients with history of previous drug abuse, as only one study reported separate data for this subgroup.
- The present data on the incidence and prevalence of dependence following the prescription of opioids to treat chronic and acute pain cannot be considered conclusive. However, the authors conclude that the available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk of developing dependence.

**Level 2a**

Clinicians should consider the use of opioids because of their proven effectiveness in treating pain and ameliorating quality of life of suffering patients—regardless of the fact that the published literature does not permit a conclusive statement about the risk of dependence. Clinical practice guidelines developed in the chronic non-cancer pain setting recommend that: 'Adherence monitoring is crucial to avoid abuse of the drugs and at the same time to encourage appropriate use, and involves the initiation of drug screening, pill counts, and patient care agreements, with the motto of "trust but verify" ' (243).

**Level 5**

#### *2.3.3.3 Opioid toxicity*

There is a wide variation in the dose of opioid that is toxic, both between individuals and over time. The ability to tolerate a particular dose depends on the degree of responsiveness of the pain to opioids, prior exposure to opioids, rate of titration of opioids, concomitant medication and renal function. Toxicity can be a frightening and even life threatening experience, but is usually reversible. Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression (244).

Patients may develop toxicity on titration of opioids however, toxicity may occur in patients who are relatively stable on long term opioid therapy. This is known as '*late opioid toxicity*'. Much of this can be explained by the role of morphine sulphate and its metabolites. Morphine sulphate is metabolised in the liver to the active metabolites morphine sulphate-3-glucuronide (M3G) and morphine sulphate-6-glucuronide (M6G) (245). M6G, which binds to opioid receptors, contributes significantly to the analgesic effect of morphine sulphate and can cause nausea and vomiting, sedation and respiratory depression (148). Symptoms mediated via M3G are impaired cognitive function, myoclonus, seizures and hyperalgesia (223). These morphine sulphate metabolites may accumulate secondary to dehydration, impaired renal function, sepsis, hepatic disease and age, as well as the chronic administration of medicines that could inhibit morphine sulphate metabolism by glucuronidation in the liver, such as benzodiazepines and barbiturates.

- Lawlor et al (2000) performed a rigorous evaluation of potential precipitants in 71 patients with opioid-induced delirium. The most frequent causes were found to be a triad of: opioid and other psychoactive medication; infection; and volume depletion or dehydration. Successful strategies were aimed at treating all of these precipitants (239).

**Level 2b**

**Management of opioid toxicity (19, 73)**

Renal and hepatic function should be checked and other causes of systemic deterioration excluded e.g. infection, hypercalcaemia. Any reversible precipitating cause should be treated.

**Level 5**

**Mild opioid toxicity**

In mild opioid toxicity:

- Reduce the dose of opioid
- Ensure adequate hydration and treat any underlying cause
- If agitation/confusion are problematic, consider a neuroleptic such as haloperidol.

**Moderate opioid toxicity**

If respiratory rate ≥ 8/min, oxygen saturations are normal and the patient is not cyanosed and is easily rousable, omit the next dose (or stop infusion/remove patch) of regular opioid immediately, and adopt a 'wait and see' approach. When the situation is more stable, either omit or reduce further doses and re-assess pain before re-introducing regular opioid therapy.

**Severe opioid toxicity**

If respiratory rate is 8/min or less, oxygen saturations are abnormal or the patient is cyanosed, urgent admission is indicated. Consider reversal of respiratory depression using naloxone; use reversing agents cautiously. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. The patient's background analgesia will subsequently need to be reviewed. Seek specialist palliative medical advice for continuing problems, particularly if transdermal patches have been used.

**Use of naloxone for reversal of opioid side-effects**

(Palliative Adult Network Guidelines 2011(19), based on the recommendations of the American Pain Society (246))

If the patient's respiratory rate is< 8/min, the patient is barely rousable/unconscious and/or is cyanosed:

- Dilute a standard ampoule containing naloxone 400 micrograms to 10ml with sodium chloride 0.9% for injection
- Administer 0.5ml (20micrograms) IV every 2 minutes, until the patient's respiratory status is satisfactory
- Further boluses may be necessary because naloxone is shorter-acting than morphine sulphate and other opioids.

Close observation is needed to ensure that the patient is breathing satisfactorily and that pain control is maintained.

If using naloxone, seek specialist advice for management of opioid side-effects and for ongoing cancer pain management.

**Recommendation 19 Opioid toxicity**
**The following are responsible for implementation of recommendation 19:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery of the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression. | |
| **Key recommendation** | |
| **D** | If toxicity is experienced on a stable dose of an opioid which has been previously tolerated, other factors should be sought and treated such as infection, dehydration, renal impairment or hypercalcaemia. |

### *2.3.4. Opioid rotation*

When prescribed opioids for cancer pain, a minority of patients will experience inadequate pain relief, persistent unacceptable side-effects, or a combination of the two, despite dose titration and management of predictable side-effects (2, 247).

- **Opioid rotation** is the term given to the clinical practice of substituting one opioid – the 'initial opioid' - with another, in order to obtain a satisfactory balance between pain relief and side-effects (226).
- **Opioid switching** is the term used to describe a change of opioid shortly after initiation of treatment, due to poor initial response to the initial opioid (248).

Although these definitions are used in the academic literature, in clinical practice the terms opioid rotation and opioid switching are used interchangeably. For the purposes of simplicity, the term 'opioid rotation' *only* will be used in these clinical guidelines.

Opioid rotation has become common practice in the management of cancer pain (249). It has been found to be necessary in approximately 20% - 44% of cancer patients (250). **Level 1a**

Data has shown that opioid rotation leads to clinical improvement in more than 50% of patients with a poor response to one opioid (251). **Level 2b**

#### *2.3.4.1 Pharmacology of opioid rotation*

The biological mechanisms for the observed beneficial effect of switching from one opioid to another are not fully understood.

- A significant factor in explaining the rationale for opioid rotation is inter-individual variability in the pharmacokinetics, pharmacodynamics, and pharmacogenetics of strong opioids (226).
- Incomplete cross-tolerance describes the phenomenon of reduced tolerance to a new opioid compared to a previously used opioid (226). This allows for a lower equivalent dose of a new opioid to achieve similar pain control as the higher dose of the initial opioid, thus potentially reducing side-effects. **Level 2a**
- The role of genetic polymorphisms in inter-individual variation in response to opioid has yet to be fully elucidated. Further research may allow prospective prediction of inter-individual response to different opioids, and strategic opioid prescribing (252). **Level 3**

- Opioids differ in their binding to mu, delta and kappa receptors, although all opioids in common clinical use appear to produce the majority of their analgesic effect through mu-opioid receptor agonism. Variations in receptor types, receptor interactions, density and binding may lead to inter-individual variation in response to opioids (248).

#### 2.3.4.2 Dose conversion ratios used for opioid rotation

*(See section 2.3.5 on relative potency ratios)*

When converting from an 'initial' opioid to a new opioid, the dose of the new opioid should depend on the relative potency ratio of the two drugs. **However, limitations in the evidence mean that relative potency ratios, and descriptions of equianalgesic doses of opioids, can only represent an approximate guide**. Clinicians must remember that opioid dose conversion ratios are not fixed but are affected by the clinical context of the switch and the setting of care. Careful monitoring during opioid rotation is required to avoid either under-dosing, leading to uncontrolled symptoms, or over-dosing, leading to undesirable side-effects. Indeed, Webster and Fine (2012) caution that increases in morbidity and mortality attributable to errors in opioid rotation have been observed in the last decade. They cite inadequate prescriber's competence, proliferation of inconsistent guidelines for opioid rotation, conflation of equianalgesic tables as conversion tables, and limitations inherent in the equianalgesic dose tables as contributory causes (253).

#### 2.3.4.3 Indications for opioid rotation

Predictable side-effects such as nausea and drowsiness on initiation of a strong opioid are expected to resolve within days, and are not an indication to opioid rotate (2). Prior to opioid rotation, it should be ensured that measures to manage side-effects have been attempted, e.g. optimising laxatives and anti-emetics (148). Where opioid rotation is being considered due to poorly controlled pain, the use of adjuvant agents or non-pharmacological interventions should be considered in addition to opioid analgesia (148). **Level 5**

If side-effects are experienced while taking a stable dose of an opioid that has previously been well tolerated, other factors contributing to opioid toxicity should be considered, such as infection, dehydration, renal impairment or hypercalcaemia (2).

Opioid rotation may be indicated in many clinical scenarios, including (254):

- In order to improve adherence to analgesia e.g. by using a more convenient route of administration such as transdermal patch, (148)
- In order to improve unacceptable opioid side-effects, including symptoms of neurotoxicity or opioid-induced hyperalgesia, (148)
- Where there has been rapid development of tolerance to an opioid, (255)
- In order to rationalise the choice of opioid, where there has been a significant change in condition e.g. development of renal failure (148).

#### 2.3.4.4 The evidence for opioid rotation

- Quigley et al conducted a Cochrane review in 2004 that examined the evidence base for the effectiveness of opioid rotation to improve drug tolerability. Fifty-two studies were included in the review, including 23 case reports, 15 retrospective studies or audits, and 14 prospective uncontrolled studies. All studies except one reported opioid switching as a beneficial clinical practice. The numbers of patients included in these studies tended to be small. At that time no randomized controlled trials or prospective controlled studies had been carried out in this area (256). **Level 2b**

- Riley et al (2006) subsequently carried out the first prospective case controlled study on opioid rotation and found that, of 186 palliative care patients, 47 patients did not achieve adequate analgesia with oral morphine sulphate. In addition, those patients whose pain did not respond to morphine sulphate experienced more side-effects such as nausea and confusion, than the morphine sulphate-responders. A single rotation to oxycodone was effective in 37 of 47 patients. Four patients required further opioid rotation, with two requiring a third change in opioid. Of the patients opioid rotated, 41 of 47 achieved a good clinical outcome, although the method of assessment of this was not reported (257). **Level 4**
- Dale et al performed an updated systematic review for the effectiveness of opioid rotation in 2011 (226). Eleven papers met the inclusion criteria; none were randomized controlled trials/meta-analyses. Studies comprised 280 patients (group size 10–32). A variety of opioids and switching strategies were studied. Pain was significantly reduced in the majority of studies. Serious adverse effects were improved.
    - The authors of the review questioned whether in some studies, up-titration of the dose of the primary opioid would have been more appropriate than opioid rotation, particularly in those patients on low doses of opioid. They concurred with Quigley et al (2006) that opioid rotation is a useful clinical strategy to manage opioid side-effects but cautioned that due to serious design limitations, the level of evidence for rotation is low. The authors recommended that randomized trials, with standardization of cohort classification, use of outcomes and analysis are warranted to establish the practice of opioid rotation (226). **Level 2a**
- Subsequently, a number of further case series and observational studies have been published. Smith and Peppin (2014) provide a review of literature up to May 21st 2013. While the studies support the practice of opioid rotation, methodological limitations persist and therefore the evidence base remains weak (258).

**Recommendation 20 Opioid rotation**
**The following are responsible for implementation of recommendation 20:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Opioid rotation utilises inter-individual variability and the phenomenon of incomplete cross tolerance in order to maximise the analgesic effect of a new opioid while minimising side effects. | |
| **Key recommendation** | |
| **B** | Opioid rotation should be performed where pain is poorly controlled, or side-effects are intolerable. Opioid rotation should only be performed by those with relevant clinical expertise. |

### *2.3.5 Opioid relative potency ratios*

As stated previously, when converting from one strong opioid to another, the initial dose of the new opioid should depend on the relative potency of the two drugs (148), as well as other clinical factors. There is a lack of evidence to support the dose conversion ratios commonly used in clinical practice (247), and therefore such relative potency ratios represent an approximate guide only. **Level 2b**

#### *2.3.5.1 Evidence for relative potency ratios*

The current available evidence is limited by several characteristics:

- Much of the current evidence on the relative potency of different opioids is derived from single-dose studies ('relative potency assays'(247)) (259, 260). These studies do not take into account the potential role of active opioid metabolites, which may contribute to analgesia or toxicity. Therefore, data from these studies may have limited applicability when opioids are used on a chronic basis such as in cancer pain (2, 247, 261). **Level 2a**
- Wide inter-individual variability in opioid pharmacokinetics, influenced by age, ethnicity, the presence of renal or hepatic impairment, and genetic variation exists (2). **Level 2b**
- The dose and duration of opioid use, direction of the opioid rotation, and concurrent medications will influence the final opioid dose required (148). **Level 5**
- The multidimensional nature of pain may also contribute to observed variability (2).
- The setting in which a patient is being managed may also influence dose conversion calculations. Where a patient is in a less intensively monitored setting, for example at home, a more conservative approach to dose conversions is recommended (247). **Level 5**

Therefore, the relative drug potency ratio used should not be a simple mathematical calculation, but should take in to account the underlying clinical situation (247). **Level 2a**

Attention to monitoring and dose titration is required, especially when: **Level 5**

- Rotating between opioids at high doses,
- When there has been a rapid recent up-titration in the dose of the primary opioid,
- When rotating to or from methadone (2, 148).

Pain control should be assessed regularly, and doses titrated as required. **Level 2a**

**Dose reduction post-opioid rotation**

To take into account the phenomenon of incomplete cross-tolerance, a dose reduction for the first 12 to 24 hours of alternative opioid should be considered, especially when rotating between high doses (2, 148). There is no definite evidence currently for the optimal percentage dose reduction, but a range from 25-50% has been suggested in the literature. **Level 5**

**Recommendation 21 Evidence for opioid relative potency ratios**
**The following are responsible for implementation of recommendation 21:**
*CEO/General/Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>There is evidence for the usefulness of opioid rotation as a clinical strategy to optimise analgesia and limit side effects. There is less robust evidence to support the relative drug potency ratios commonly used in practice. | |
| **Key recommendation** | |
| **D** | Evidence-based relative potency ratios should be applied, taking into account individual patient factors. Pain control should be assessed regularly and doses titrated as required. |

**Relative potencies of individual opioids – the current evidence**
*Note – most relative potencies relate to the relative potency of a strong opioid in relation to morphine sulphate. When switching from a strong opioid other than morphine sulphate, it may be necessary to convert the dose of the initial opioid to the oral morphine sulphate equivalent dose, and then use this to determine the dose of the new opioid (148).*

**Codeine**
Codeine is one-tenth as potent as oral morphine sulphate (19, 148). **Level 5**

**Tramadol**
By injection, tramadol is approximately one-tenth as potent as parenteral morphine sulphate (148, 262). With regard to oral tramadol, the manufacturers recommend a relative potency ratio of 1 : 6-10 for oral morphine sulphate to oral tramadol. In contrast, RCT evidence indicates a relative potency ratio for oral morphine sulphate to oral tramadol of 1 : 4-5, i.e. tramadol 100mg po = morphine sulphate 20-25mg po (148, 263, 264). **Level 2b**

**Oxycodone**
Different relative potency ratios have been reported in multiple dose settings (2).

The manufacturers recommend a relative potency ratio of 2 : 1 when converting from oral morphine sulphate to oral oxycodone i.e. to halve the dose of morphine sulphate to obtain the equivalent potency dose of oxycodone. This ratio has commonly been used in clinical practice. **Level 5**

- This recommendation was supported by a double-blinded RCT performed by Curtis et al in 1999. It compared doses of 20mg or 40mg of oxycodone to doses of 45mg or 90mg of morphine sulphate in 169 women post-hysterectomy, and found that analgesic effect was comparable (2, 265).

- In 1998, Bruera et al (167) performed a randomised, blinded, cross-over study involving 32 adult patients with cancer pain, in order to compare the efficacy of oxycodone and morphine sulphate. Patients were randomised to controlled-release oxycodone, or controlled-release morphine sulphate, for seven days, and then crossed-over to the alternate drug for a further seven days. In order to blind the study using available tablet strengths, the dose ratio of oral morphine sulphate to oral oxycodone was set at 1.5 : 1. No significant differences in pain scores or side-effects were noted. The median morphine sulphate : oxycodone dose ratio was 1.5 : 1. **Level 2a**
- Mercadante et al (2011) performed a systematic review of the evidence regarding the relative potency of oxycodone compared to other strong opioids (247). Four randomised, double-blind, crossover trials, and two uncontrolled cohort studies were identified. In the four randomised cross-over trials, involving 198 patients, patients were stablised in an entry phase using either immediate release morphine sulphate (266), modified release oral oxycodone and modified release oral morphine sulphate (164, 167), or oral oxycodone and a morphine sulphate intravenous patient-controlled analgesia infusion (166). Different mean daily doses of oral oxycodone were compared in each study, with the mean daily doses of oral oxycodone ranging from 40mg (266) to 193mg (167). The final morphine sulphate : oxycodone potency ratios demonstrated ranged from 1.3 : 1 (166) to 1.8 : 1. Thus, these four cross-over trials found evidence to support a conversion ratio of 1.5 : 1 between morphine sulphate and oxycodone (266, 247). **Level 1b**
- Further evidence is available from the uncontrolled cohort studies included in the systematic review. Patients were switched to oral oxycodone due to poor pain relief and side-effects. In the first cohort study, 74% of patients were reported to have successfully switched from oral morphine sulphate to oral oxycodone using a ratio of 2 : 1 (257). In the second cohort study, an oral morphine sulphate : oral oxycodone ratio of 1.5 : 1 was used initially. However, patients required subsequent up-titration of the oral oxycodone dose, leading to a higher oral oxycodone dose, approximating a ratio of 1 : 1 with oral morphine sulphate, when stable analgesia was achieved (267). **Level 2b**

**Recommendation 22 Relative potencies: oxycodone**
**The following are responsible for implementation of recommendation 6:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Despite limitations, there is evidence from randomised controlled trials to support the use of a conversion ratio of oral morphine sulphate to oral oxycodone of between 1.5 : 1 and 2 : 1. | |
| **Key recommendation** | |
| **B** | A relative potency ratio of oral morphine sulphate to oral oxycodone of between 1.5 : 1 and 2 : 1 is recommended. |

**Hydromorphone**

The manufacturers recommend a relative potency ratio for oral morphine sulphate: oral hydromorphone of 7.5 : 1 when the sustained release preparation is used, and of 7.7 : 1 when the immediate release preparation is used.

- Hagen et al performed a randomised controlled crossover study comparing the relative potencies of oral morphine sulphate and oral hydromorphone. This demonstrated that 124mg of oral morphine sulphate was equivalent to 30mg oral hydromorphone (ratio of 4.13 : 1) (247, 268). **Level 3**
- A Cochrane systematic review performed by Quigley et al in 2002 regarding the evidence for the analgesic effect of hydromorphone identified 43 studies comprising 2725 patients. This review was unable to determine a specific equianalgesic ratio between morphine sulphate and hydromorphone due to the heterogeneity of the studies included (2, 269).
- Mercadante et al (2011) in a systematic review of opioid conversion ratios identified three case series of patients with both malignant and non-malignant pain, who were rotated from a variety of initial opioids to oral hydromorphone sustained-release preparations (247, 270-272).

  In the first case series, 239 patients were converted to oral hydromorphone from the oral morphine sulphate equivalent dose of several different initial opioids, using a relative potency ratio of oral morphine sulphate to oral hydromorphone of 8 : 1 (272). Further uptitration of the subsequent oral hydromorphone dose was required in 54% of patients. No data is available specifically on the cancer patients within these case series. **Level 2a**

  In the two other case series, of 85 and 56 patients respectively,(270, 271) a conversion ratio from oral morphine sulphate, or the oral morphine sulphate equivalent dose of another opioid, to oral hydromorphone of 5 : 1 was used. The oral hydromorphone dose required uptitration in order to achieve analgesia in 23% of patients in one study (271) and in 80% of patients in the other study (270).

  In all three case series, an improvement in pain control was obtained after switching to oral hydromorphone, after titration to effect (247).

  Based on the evidence of this systematic review, the authors recommend a conversion ratio of oral morphine sulphate to oral hydromorphone of 5 : 1, and of oral oxycodone to oral hydromorphone of 4 : 1(247). They conclude in making a weak recommendation to use a conversion ratio for oral morphine sulphate to oral hydromorphone of 5 : 1 (247). **Level 1b**

**Recommendation 23 Relative potencies: hydromorphone**
**The following are responsible for implementation of recommendation 23:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| Key recommendation | |
|---|---|
| C | A relative potency ratio of oral morphine sulphate to oral hydromorphone of 5 : 1 is recommended. |

**Buprenorphine**
Buprenorphine is known to be a partial mu-agonist, and to have a slow receptor dissociation that could potentially impede the full effectiveness of other co-administered opioids (247). The manufacturers recommend a relative potency ratio of oral morphine sulphate to transdermal buprenorphine of 70 – 115 : 1 (148).

- Mercadante et al performed a systematic review in 2011, examining the relative potency ratio of buprenorphine compared to other strong opioids (247). Only three studies met the inclusion criteria, of which two were '*n of 1*' studies. In the first, a prospective cohort study of 32 patients, 16 patients were rotated from transdermal buprenorphine to transdermal fentanyl and 16 were rotated in the opposite direction (273). Improvements in analgesia and side-effects were noted in both groups. The relative potency ratios calculated varied depending on the direction of opioid rotation (transdermal fentanyl to transdermal buprenorphine ratio was 1:0.7; transdermal buprenorphine to transdermal fentanyl was 2.8:1). The study was limited by patient selection and the methodology prevented meaningful conclusions being drawn regarding conversion ratios (247, 273).

  The two '*n of 1*' studies (247, 274, 275) were performed in patients with stable controlled pain, who were rotated from oral morphine sulphate or transdermal fentanyl to transdermal buprenorphine. The first study (274) demonstrated that patients on a stable dose of morphine sulphate could be safely switched from oral morphine sulphate to transdermal buprenorphine using a relative potency ratio of 70:1. The second study demonstrated that cancer patients receiving a stable dose of either transdermal fentanyl or buprenorphine could be safely rotated to the alternative transdermal opioid using a relative potency ratio of transdermal fentanyl to transdermal buprenorphine of 0.6:0.8. **Level 2b**

  The authors of the systematic review conclude that 0.8mg of transdermal buprenorphine is equipotent to 60mg of oral morphine sulphate (ratio 1:75) or 0.6mg of transdermal fentanyl (ratio 1.3:1).

- Skaer performed a narrative review of the evidence in 2014, and found that the current evidence supports the use of a ratio for the conversion of buprenorphine to morphine sulphate of 1:75 (216). **Level 5**

**Recommendation 24 Relative potencies: buprenorphine**
**The following are responsible for implementation of recommendation 24:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding** | |
|---|---|
| Buprenorphine is a partial mu-receptor agonist and a partial kappa-receptor antagonist and has slow receptor dissociation that may impede the full effectiveness of other opioids used. Evidence is limited regarding the equipotency of transdermal buprenorphine and other opioids. | |
| **Key recommendation** | |
| **C** | A relative potency ratio of oral morphine sulphate to transdermal buprenorphine of 75 : 1 is recommended. |

**Fentanyl**

Fentanyl is most commonly used via a transdermal patch (2) and in patients with stable pain where the oral route is not possible or not convenient (also see section 2.3.2 on route of administration). It is recommended that an interval of at least three days should be used between dose changes for dose titration (2, 276). **Level 3**

On switching from an oral opioid to a transdermal fentanyl:

- if taking a 4 hourly oral opioid, continue for 12 hours after applying the fentanyl patch
- if taking a 12 hourly oral opioid, the last dose should be given when the patch is applied (2).

On removal of the transdermal fentanyl patch, serum fentanyl concentrations fall by 50% in 16 hours (277). Therefore, a short acting opioid should be used, as needed, for the first 24 hours until fentanyl clears, at which point a long acting formulation of an alternative opioid may be commenced regularly. In patients who are close to death, the patch should be left in situ and additional analgesia used as required (2). **Level 5**

The manufacturers recommend a relative potency ratio for oral morphine sulphate to transdermal fentanyl of 150:1, when the dose of oral morphine sulphate or equivalent opioid has been stable for a number of weeks. A morphine sulphate : fentanyl ratio of 100:1 is recommended for highly opioid-tolerant patients who have been on strong opioids for a long period of time.

- In order to evaluate the relative potency of fentanyl compared to other strong opioids, Mercadante et al (2011) performed a systematic review of the evidence (247). Six studies were identified, one of which could not be used due to unclear information. The patient population included in the remaining five studies was 457. Most patients were switched from oral morphine sulphate to transdermal fentanyl.
- One of these studies, by Donner et al (1996), was a cohort study of 98 patients. It aimed to identify what dose of transdermal fentanyl was equivalent to an oral dose of morphine sulphate which had been titrated to achieve stable analgesia (247, 278). An initial equivalent dose of transdermal fentanyl was calculated using an oral morphine sulphate : transdermal fentanyl ratio of 100:1. It was found that, after switching, this had to be increased in 58% of patients in order to achieve adequate pain control. A regression analysis demonstrated a mean relative potency ratio between the oral morphine sulphate dose and the final, effective, transdermal fentanyl dose of 70:1 (278). **Level 2b**

Manufacturers recommend a conversion ratio from oral morphine sulphate to transdermal fentanyl of 100 - 150 : 1 (247). On the basis of the above systematic review, Mercadante et al (2011) conclude that a ratio of oral morphine sulphate to transdermal fentanyl of 100 : 1 appears to avoid or reduce the risk of either under or over-dosing (247).

**Recommendation 25 Relative potencies: fentanyl**
**The following are responsible for implementation of recommendation 25:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| Key recommendation | |
|---|---|
| C | A relative potency ratio of oral morphine sulphate to transdermal fentanyl of 100 : 1 is recommended. |

**Alfentanil**
Alfentanil is one-quarter as potent as fentanyl (279,148). **Level 2b**

Alfentanil is approximately 30 times as potent as oral morphine sulphate (148).

Most available clinical practice guidelines recommend a relative potency ratio from oral morphine sulphate to subcutaneous alfentanil of 32 : 1. This is based on evidence from the use of alfentanil in the anaesthetic setting. Due to the high potency of alfentanil, caution is recommended in converting doses. **Level 5**

**Methadone**
Conversion ratios from morphine sulphate and other opioids to methadone are variable, and relative potency ratios for oral morphine sulphate : oral methadone quoted in the available literature range from 5 : 1 to 10 : 1 (247).

The relative potency ratio of methadone when converting from other strong opioids has been shown to depend on a number of factors, including the reason for switching opioids, and the route and method of switching. Importantly, the ratio also varies according to the direction of the switch (2).

For patients with stable pain who are being switched due to adverse effects, a high relative potency ratio leading to a relatively lower methadone dose has been recommended. Patients with uncontrolled pain may potentially require a lower conversion ratio and a higher subsequent comparable dose of methadone (247, 280). **Level 1b**

- Bruera et al (2004) performed a double-blind, parallel study comparing the effectiveness of oral morphine sulphate and oral methadone, over 28 days, in 103 patients with moderate or severe cancer pain (170, 186). A relative potency ratio of oral morphine sulphate to oral methadone of 2 : 1 was used. This resulted in excess adverse effects, including sedation, and a high drop-out rate due to side-effects in the methadone group (170, 186). A morphine sulphate : methadone relative potency ratio of no less than 4 : 1 was therefore suggested by the authors in order to limit side-effects (186). **Level 2a**
- In a systematic review performed by Mercadante et al (2011),(247) it was found that all available studies examining rotation to methadone from other opioids had serious methodological limitations and none used a method which was specifically designed to evaluate actual equivalent methadone doses under controlled conditions (247). In common with other studies, this review found that higher oral morphine sulphate-equivalent doses required a higher conversion ratio and lower subsequent doses of oral methadone (247).
- In a systematic review and meta-analysis of the dose ratios between oral morphine sulphate and oral methadone carried out by Weschules et al (2008),(281) the meta-analysis demonstrated a median relative potency ratio of oral morphine sulphate : oral methadone of 8.25 : 1. Relative potency ratios within individual studies varied widely, but the meta-analysis demonstrated a strong positive correlation between the oral morphine sulphate dose prior to switching and the subsequent oral methadone dose. **Level 2a**

Two suggested methods for dose conversion ratios are outlined: the NCCN, or Ayonride conversion chart and the Plonk equation. The Plonk equation is a linear equation based on clinical experience and data from 5 published articles. The dose of oral morphine equivalent / day divided by 15, plus 15 to give the methadone dose / day (282). A suggested guideline for dose conversion ratios is outlined in table 8.

**Table 8** Oral morphine sulphate dose conversion to oral methadone (adapted from NCCN Guidelines (52))

| Oral morphine sulphate | Dose conversion ratio to oral methadone (oral morphine sulphate : oral methadone) |
|---|---|
| 30 – 90mg | 4 : 1 |
| 91 – 300mg | 8 : 1 |
| > 300mg | 12 : 1 |

**Level 5**

It is important to note that the above conversion ratios do NOT apply when converting from methadone to an *alternative* strong opioid. This is due to the highly lipophilic nature of methadone and the long elimination half-life which results (52). **Level 5**

On discontinuation of methadone, a conservative ratio for oral morphine sulphate : oral methadone of 1 : 1 may be used, and supplemented with additional short acting morphine sulphate as needed. The dose of morphine sulphate or other strong opioid will require frequent dose adjustment and uptitration in the following days as methadone clears (52, 283). **Level 4**

The use of methadone is challenging due to its unique pharmacological properties in comparison to most other opioids used for cancer pain. Methadone use outside of the specialist setting is not recommended (2).

**Methods of rotating from morphine sulphate or other strong opioids to methadone**

When rotating strong opioids to methadone, various methods of rotation have been proposed (284). The most commonly used methods are the 'stop and go' (SAG) method, and the 'three day switch' (3DS) method. There is no consensus at present as to the optimal method (285). **Level 5**

In the SAG method, the initial opioid is immediately replaced by methadone. The SAG method may utilise methadone as needed for the initial five days (the 'ad libitum' method) or switch the total daily oral morphine sulphate dose directly to an equianalgesic dose of methadone from day one (the 'rapid conversion' method).

The 'ad libitum' method is also known as the Morley and Makin method (286, 287) and was initially proposed in 1998 for initial morphine sulphate doses greater than 300mg / day (287). Using this method, the initial opioid is discontinued and methadone of one-tenth of the total daily morphine sulphate dose in mg is prescribed up to a maximum of 30mg per dose. This is given as needed up to, but not more than, three hourly. For example, if a patient is taking 50mg of morphine sulphate twice daily prior to conversion, 10mg of methadone, as needed, would be prescribed. On day six, or when methadone requirements have stabilised, the total daily methadone requirement is divided into two daily doses, given regularly.

A modified Morley and Makin method has been proposed in some clinical guidelines, (148) where an initial dose of 1/10$^{th}$ of the previous oral daily morphine sulphate requirement is given as methadone, and the subsequent as-needed methadone dose is calculated as 1/30$^{th}$ of the previous total daily oral morphine sulphate dose, to a maximum of 30mg. No clinical trials looking specifically at this method were identified in the literature search performed for the purposes of this clinical guideline. A case series (288) reports that modification of this method with a 30% reduction in the methadone dose was effective with no excess adverse effects reported.

The 'rapid conversion' SAG method, involves converting the initial opioid total daily dose into an equianalgesic daily methadone dose, from day one of the switch (284).

In the 3DS method, the dose of the initial opioid is reduced stepwise by one-third every day, and substituted with an equianalgesic dose of methadone over three days. The equianalgesic dose of methadone may be calculated using relative potency ratios such as outlined in Table 8.

Advocates for the SAG method argue that a rapid switch gives faster onset of analgesia and reduction of adverse events, while it is proposed that the 3DS method avoids methadone accumulation and early toxicity, in particular in patients on high doses (284). **Level 5**

Data on the efficacy and safety of the two methods has to date been based on small case series. Tse et al (2003) (286) performed a prospective study of the 'ad libitum' SAG method in 37 adult cancer patients who had uncontrolled pain, or intolerable side-effects with morphine sulphate. Twenty seven patients completed the study, with 24 (88.65%) reported to reach good pain control by day 7. The median time to achieve good pain control was three days (median one to 11 days) (286). **Level 2b**

However, the efficacy and safety of the 'ad libitum' SAG method has been disputed by some advocates of the 'rapid conversion' SAG method. In particular, Mercadante (2004),(289) in a letter published in response to the study performed by Tse et al (286), suggests that this method does not fit with the unique pharmacokinetics of methadone and may result in a temporary under-treatment of pain. Due to methadone's large volume of distribution, it requires a 'priming' dose to reach an effective concentration before stable analgesia is achieved. Mercadante questions whether 11 days is an unacceptably long delay in achieving effective pain control in this group of patients (289).

**Level 5**

- Moksnes at al (2011) performed a randomised study in order to evaluate the efficacy and safety of the 'rapid conversion' SAG strategy compared to the 3DS method, when switching from morphine sulphate or oxycodone to methadone in cancer patients (284). Forty two adult cancer patients were randomised to either 'rapid conversion' SAG or 3DS. The mean pre-switch morphine sulphate equivalent dose was 900mg / day in the SAG group and 1330mg / day in the 3DS group, but the groups were otherwise matched. In the SAG group, the current daily opioid dose was replaced by an estimated equianalgesic daily dose of methadone, using a dose-dependent switching table. The relative potency ratios between oral morphine sulphate and oral methadone used ranged from 4 : 1 at the lowest morphine sulphate doses, to 12 : 1 at the highest morphine sulphate doses. The rescue dose was one-sixth of the total daily dose and no titration of methadone was performed until day five. The 3DS group were converted to methadone in stages, as described above, over three days.

  There was no significant difference identified between the two groups in the mean average pain intensity on day 3 (mean difference 0.5; SAG 4.1 and 3DS 3.6). The 'rapid conversion' SAG group had more dropouts (seven) and three significant adverse events (two deaths, and one episode of severe sedation). No severe adverse events were observed in the 3DS group. Although only 28 patients completed the study, the authors concluded that the 'rapid conversion' SAG group reported a trend of more pain at day 3, and had significantly more dropouts and severe adverse events, indicating that the 'rapid conversion' SAG method should not replace the 3DS method when switching from high doses of morphine sulphate to methadone (284).

**Level 1b**

However, the Moksnes et al study only addresses the 'rapid conversion' SAG approach. The 'ad libitum' SAG approach, such as that described by Tse et al, (286) or by Morley and Makin in 1997, (287) has been shown to be effective and safe in small, non-randomised studies, but no randomised trials have been performed.

**Level 2b**

On the basis of the best available evidence, which is of low quality, the SAG 'ad libitum' method appears efficacious, although may risk a delay in achieving effective analgesia. A systematic review and clinical guideline published in 2014 also recommends the use of the ad libitum method of switching, based on expert opinion (290). The 'rapid conversion' SAG method may risk adverse events such as sedation, particularly at high opioid doses. The 3DS method has been shown to be safer than this method (284). No RCT comparing the safety and efficacy of the 'ad libitum' SAG method and the 3DS method is available in the published literature.

**Level 1b**

**Recommendation 26 Relative potencies: methadone**
**The following are responsible for implementation of recommendation 26:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>The relative potency ratio from morphine sulphate : methadone increases as the dose of morphine sulphate increases.<br><br>When switching back from methadone to morphine sulphate, a conservative ratio of 1:1 should be used initially, and the dose of morphine sulphate uptitrated as required.<br><br>With regard to methods for switching to methadone from another strong opioid over another, there is not enough evidence to determine the superiority of one method over another. The 'ad libitum' stop and go (SAG) method and the 3 day switch (3DS) methods both appear safe and efficacious in small, non-randomised studies. The 'rapid conversion' SAG method appears to risk excess toxicity at high opioid doses. | |
| **Key recommendations** | |
| **C** | **26.1** Consensus-based relative potency ratios should be utilised when switching from a strong opioid to methadone, and doses should be titrated up or down following the switch. |
| **D** | **26.2** Methadone is a complex strong analgesic agent and should be used under specialist supervision only. |

**Opioid rotation: conclusions**

Opioid switching is a useful therapeutic tool, used in order to maximise analgesia and limit side-effects. The relative potency ratios used to convert doses should take into account the clinical context and the needs of the individual patient (247).

**Level 2a**

It is difficult to reproduce complex clinical situations in randomised controlled blinded trials, but prospective studies provide good evidence for predictable conversion ratios between oral hydromorphone, oral morphine sulphate, oral oxycodone and transdermal fentanyl (247).

Opioid switching to methadone requires expertise, and requires frequent re-evaluation to adjust opioid doses (247, 260). Randomised controlled studies are required to provide definitive recommendations based on more solid evidence (247).

**Level 3**

## Opioid equivalence tables

***Note:*** Opioid equivalence tables should only be used as an approximate guide.

**Tables 9,10 and 11 represent Grade C recommendations**

**Table 9** Weak opioids – Equivalence to oral morphine sulphate

| Codeine | Morphine sulphate | Tramadol |
|---|---|---|
| **24 hr total oral dose (mg)** | **24 hr total oral dose (mg)** | **24 hr total oral dose (mg)** |
| 60mg | 6 | 50 |
| - | 10 | 100 |
| 240mg | 20 | 200 |
| - | 30 | |
| - | 40 | 400 |
| - | 50 | |
| - | 60 | |
| - | 70 | |
| - | 80 | |

**Table 10** Strong opioids – Equivalence to oral morphine sulphate

| **Morphine sulphate** | **Oxycodone** | **Hydromorphone** | **Buprenorphine** | **Fentanyl** | **Morphine sulphate** |
|---|---|---|---|---|---|
| *24 hr total oral dose (mg)* | *24 hr total oral dose (mg)* | *24 hr total oral dose (mg)* | *Dose / hr (mcg) transdermal* | *Dose / hr (mcg) transdermal* | *24 hr total oral dose (mg)* |
| 10 | - | - | 5 | - | 10 |
| 20 | - | 4 | 10 | 12 | 20 |
| 30 | 20 | 6 | | | 30 |
| 40 | | 8 | 20 | 18 | 40 |
| 50 | - | 10 | | | 50 |
| 60 | 40 | 12 | 35 | 25 | 60 |
| 70 | | 14 | | | 70 |
| 80 | | 16 | | 37 | 80 |
| 90 | 60 | 18 | 52.5 | | 90 |
| 100 | | 20 | | | 100 |
| 110 | | - | | 50 | 110 |
| 120 | | 24 | | | 120 |
| 130 | 80 | - | 70 | | 130 |
| 140 | | 28 | | 62 | 140 |
| 150 | | - | | | 150 |
| 160 | 100 | 32 | | | 160 |
| 170 | | - | - | 75 | 170 |
| 180 | | 36 | - | | 180 |
| 190 | | - | - | | 190 |
| 200 | | - | - | 87 | 200 |
| 210 | - | 42 | - | | 210 |
| 220 | 150 | - | - | | 220 |
| 230 | | - | - | 100 | 230 |
| 240 | | 48 | - | | 240 |
| 250 | | - | - | | 250 |
| 260 | | 52 | - | | 260 |
| 270 | | - | - | | 270 |
| 280 | | 56 | - | 150 | 280 |
| - | - | - | - | | - |
| - | - | - | - | | - |
| 360 | 240 | 72 | - | | 360 |

**Table 11** Processes for converting opioids

| Converting From | Converting To | Process |
|---|---|---|
| **Oral (mg)** | **Oral (mg)** | |
| Codeine | Morphine sulphate | Divide by 10 |
| Tramadol | Morphine sulphate | Divide by 5 – 10 |
| Morphine sulphate | Oxycodone | Divide by 1.5 – 2 |
| Morphine sulphate | Hydromorphone | Divide by 5 |
| **Oral (mg) / 24 hours** | **Subcutaneous / 24 hours** | |
| Morphine sulphate | Fentanyl (mcg) | Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs. |
| Morphine sulphate | Alfentanil (mg) | Divide by 32 |
| **Oral (mg) / 24h hours** | **Transdermal (mcg / hour)** | |
| Morphine sulphate | Buprenorphine | Divide by 75 to obtain equivalent buprenorphine dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength. |
| Morphine sulphate | Fentanyl | Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength. |
| | Alternatively, use Table 10 to obtain closest appropriate patch strength | |

## Opioid Equivalence Summary Table

Guidelines for use:

- relative potency ratios should only be used as an approximate guide (2b) and individual and clinical factors should be taken into account (2a)
- on opioid rotation, particularly at high doses, a dose reduction of 25 – 50% should be considered to account for incomplete cross-tolerance (5)
- pain control should be assessed regularly, and doses titrated as required.

**Table 12** Opioid Equivalence Summary Table
(all recommendations Grade C)

<table>
<tr><th colspan="2">Morphine</th><th>Codeine</th><th>Tramadol</th><th colspan="2">Oxycodone</th><th colspan="2">Hydromorphone</th><th colspan="2">Buprenorphine</th><th>Fentanyl</th><th colspan="2">Morphine</th></tr>
<tr><td colspan="2">(mg / 24 hrs)</td><td>(mg / 24 hrs)</td><td>(mg / 24 hrs)</td><td colspan="2">(mg / 24 hrs)</td><td colspan="2">(mg / 24 hrs)</td><td>(mcg / hour) Butrans®</td><td>(mcg / hour) Transtec®</td><td>(mcg / hour)</td><td colspan="2">(mg / 24 hrs)</td></tr>
<tr><th>Oral</th><th>S/C</th><th>Oral</th><th>Oral</th><th>Oral</th><th>S/C</th><th>Oral</th><th>S/C</th><th colspan="2">Transdermal</th><th>Transdermal</th><th>Oral</th><th>S/C</th></tr>
<tr><td>5</td><td>2.5</td><td>60</td><td>50</td><td>-</td><td>-</td><td>-</td><td>-</td><td colspan="2">-</td><td rowspan="2">-</td><td>5</td><td>2.5</td></tr>
<tr><td>10</td><td>5</td><td>120</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td><td>5</td><td rowspan="4">See Butrans®</td><td>10</td><td>5</td></tr>
<tr><td>20</td><td>10</td><td>240</td><td rowspan="2">200</td><td>-</td><td>-</td><td>4</td><td>2</td><td rowspan="2">10</td><td rowspan="3">12</td><td>20</td><td>10</td></tr>
<tr><td>30</td><td>15</td><td rowspan="11">Titrate to strong opioid</td><td rowspan="2">20</td><td rowspan="2">10</td><td>6</td><td>3</td><td>30</td><td>15</td></tr>
<tr><td>40</td><td>20</td><td rowspan="4">400</td><td>8</td><td>4</td><td rowspan="2">20</td><td rowspan="3">18</td><td>40</td><td>20</td></tr>
<tr><td>50</td><td>25</td><td>-</td><td>-</td><td>10</td><td>5</td><td>50</td><td>25</td></tr>
<tr><td>60</td><td>30</td><td rowspan="3">40</td><td rowspan="3">20</td><td>12</td><td>6</td><td rowspan="6">See Transtec®</td><td rowspan="3">35</td><td rowspan="2">25</td><td>60</td><td>30</td></tr>
<tr><td>70</td><td>35</td><td>14</td><td>7</td><td>70</td><td>35</td></tr>
<tr><td>80</td><td>40</td><td>16</td><td>8</td><td rowspan="3">37</td><td>80</td><td>40</td></tr>
<tr><td>90</td><td>45</td><td rowspan="6">Titrate to strong opioid</td><td rowspan="4">60</td><td rowspan="4">30</td><td>18</td><td>9</td><td rowspan="4">52.5</td><td>90</td><td>45</td></tr>
<tr><td>100</td><td>50</td><td>20</td><td>10</td><td>100</td><td>50</td></tr>
<tr><td>110</td><td>55</td><td>-</td><td>-</td><td rowspan="3">50</td><td>110</td><td>55</td></tr>
<tr><td>120</td><td>60</td><td>24</td><td>12</td><td>120</td><td>60</td></tr>
<tr><td>130</td><td>65</td><td rowspan="3">80</td><td rowspan="3">40</td><td>-</td><td>-</td><td rowspan="3">70</td><td>130</td><td>65</td></tr>
<tr><td>140</td><td>70</td><td>28</td><td>14</td><td rowspan="3">62</td><td>140</td><td>70</td></tr>
<tr><td>150</td><td>75</td><td>-</td><td>-</td><td>150</td><td>75</td></tr>
<tr><td>160</td><td>80</td><td rowspan="5">100</td><td rowspan="5">50</td><td>32</td><td>16</td><td>160</td><td>80</td></tr>
<tr><td>170</td><td>85</td><td>-</td><td>-</td><td colspan="3" rowspan="3">Consider the use of an alternative opioid</td><td rowspan="3">75</td><td>170</td><td>85</td></tr>
<tr><td>180</td><td>90</td><td>36</td><td>18</td><td>180</td><td>90</td></tr>
<tr><td>190</td><td>95</td><td>-</td><td>-</td><td>190</td><td>95</td></tr>
<tr><td>200</td><td>100</td><td>-</td><td>-</td><td>-</td><td>200</td><td>100</td></tr>
</table>

| Converting From | Converting To | Process |
|---|---|---|
| **Oral** | **Oral** | |
| Codeine | Morphine sulphate | Divide by 10 |
| Tramadol | Morphine sulphate | Divide by 5 – 10 |
| Morphine sulphate | Oxycodone | Divide by 1.5 – 2 |
| Morphine sulphate | Hydromorphone | Divide by 5 |
| **Converting From** | **Converting To** | **Process** |
| **Oral (mg / 24 hrs)** | **S/C (mg / 24 hrs)** | |
| Morphine sulphate | Alfentanil | Divide by 32 |

### *2.3.6. Managing cancer pain in patients with a history of addiction*

#### *2.3.6.1 Background and evidence*

Addiction is a syndrome and pattern of substance misuse, with biological, psychological and social aspects (291). A history of addiction to opioids, such as heroin, may compromise the effective control of cancer pain (291). In addition, patients may be receiving treatment for an addiction, such as methadone maintenance therapy (MMT), which may further complicate management. **Level 3**

Important points to note are as follows:

- Long term opioid exposure, such as that from heroin or MMT, may induce neuroplastic changes such as tolerance, and hyperalgesia (292). Cross-tolerance occurs between different opioids (292). Hyperalgesia describes increased pain sensitivity resulting from up-regulation of pro-nociceptive systems such as excitatory NMDA receptors (292). Repeated episodes of under treatment of acute pain may lead to decreased responsiveness to opioid analgesic (293). Pain may also be exacerbated by subtle withdrawal symptoms, sleep disturbance, and affective changes characteristic of the syndrome of addiction (294). **Level 3**
- Psychological features of addiction include distress avoidance, learnt behaviour and chemical coping (291). The use of alcohol and benzodiazepines has been identified as a poor prognostic indicator for cancer pain control (206). Patients with a history of addiction may have co-morbidities such as depression and anxiety, further complicating management of their physical pain (291). **Level 4**
- Social aspects influencing care include a complex social milieu, social exclusion and reduced opportunities (291). The resonance of addiction through generations of families may have implications for bereavement follow up (291). **Level 5**
- Patients' relationships with healthcare professionals may be eroded by unrealistic expectations of the patient and concerns of the physician regarding the potential for side-effects, drug diversion, or iatrogenic worsening of addiction (291).

For information on the risk of developing dependence to opioids when prescribed for cancer pain in the general population, see section 2.3.3.2.

#### *2.3.6.2 Assessment*

Assessment of pain in patients with a history of substance misuse should include consideration of the following (242, 291):

- A full substance misuse and medication history should be taken, including over-the-counter preparations
- The presence of co-dependence on substances e.g. alcohol or benzodiazepines,
- The presence of psychiatric co-morbidities e.g. anxiety or depression
- An awareness of potential barriers to effective assessment such as a reluctance of the patient to disclose substance misuse due to anxiety that their pain may not be adequately treated (291)
- An awareness of the potential for pseudo-addiction: the phenomenon of patients who seek alternate sources, or increased doses, of analgesia, as they fail to obtain adequate analgesic relief with doses prescribed (295). A defining characteristic of this syndrome is that sufficient pain relief eliminates the patient's need to self-medicate (295). **Level 3**

### 2.3.6.3 Analgesic drug selection: general principles

Cancer pain in patients with a history of addiction should be managed according to the principles of cancer pain management outlined elsewhere in this document.

General principles apply in order to reduce the risk of drug diversion or precipitation of relapse of addiction:

- Short acting drugs such as transmucosal fentanyl preparations and pethidine should be avoided, as in theory these have greater abuse potential than longer acting preparations (291)
- Sustained release tablets can be less easily crushed and injected than non-sustained release tablets (291).

**Level 5**

### 2.3.6.4 Management: general principles

A treatment agreement should be agreed at the outset with the patient, either in writing or verbally. A multidisciplinary team approach, including the involvement of addiction services should be employed. Optimally, the use of non-pharmacological interventions such as brief counseling should be used. Regular assessment of the 'Four A's' should occur: analgesia, activity, adverse effects, aberrant behavior (296).

**Recommendation 27 General principles of cancer pain management in patients with a history of addiction**

**The following are responsible for implementation of recommendation 27:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer and a history of substance misuse are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Physical, psychological, and social factors may compromise the management of cancer pain in patients with a history of substance misuse, in particular those with a history of opioid abuse or on methadone maintenance therapy. | |
| **Key recommendation** | |
| **D** | In patients with a history of addiction, short acting formulations such as transmucosal fentanyl preparations should be avoided due to their greater abuse potential.<br><br>Cancer pain assessment and management principles as outlined elsewhere in this document should be used to guide the management of cancer pain in individuals with a history of substance misuse. However, management should be modified if required and take into consideration the biological, social, and psychological features of the syndrome of addiction.<br><br>A multidisciplinary approach that involves Addiction Services should be adopted. |

#### *2.3.6.5 Co-prescribed medications: issues to consider when prescribing opioids for analgesia*

Buprenorphine is a partial agonist at mu-receptors and may be used either for its analgesic effect (usually in transdermal patch form) or as opioid substitution therapy in the management of opioid addiction. Buprenorphine should not be prescribed as an analgesic to patients receiving full mu-receptor agonists (e.g. methadone) as withdrawal may be precipitated. Similarly, patients taking high dose buprenorphine may be refractory to the analgesic effects of other co-administered opioids (291).

**Level 5**

Naltrexone is a long-acting opioid antagonist used as a therapy for **opioid** addiction. Patients receiving naltrexone are likely to be refractory to opioid analgesia. If opioid analgesia is required, a continuous infusion is required to displace naltrexone from the opioid receptors. Close monitoring, under specialist supervision, is required due to the high risk of opioid toxicity that results when the naltrexone is displaced from the receptors (291).

Methadone is a synthetic strong opioid, which acts at both mu- and NMDA receptors (294). Methadone is used as an analgesic in cancer pain management, but also as an opioid substitution therapy in the treatment of opioid addiction (methadone maintenance therapy, MMT). Chronic MMT leads to neuroplastic changes at opioid receptors, and increased tolerance and refractoriness to analgesia from opioids other than methadone (297). When opioids other than methadone are used for analgesia, MMT should be continued, as abrupt discontinuation may precipitate an acute pain crisis (298).

**Level 3**

**Level 5**

Methadone has itself been shown to be an effective analgesic agent in the management of cancer pain (280). However, while methadone has a long and variable half-life, its duration for analgesia is only 4 – 9 hours, therefore once daily dosed MMT will not provide sustained analgesia (299). As an analgesic agent, methadone's long and variable half-life, and the variable potency ratios between methadone and other strong opioids, may pose practical challenges. It should be used as an analgesic agent only with specialist palliative care or pain team supervision (280, 294).

**Level 5**

For any patient receiving opioid substitution therapy or naltrexone, consultation with the patient's addiction services and primary care team is necessary in order to ensure safe prescribing (291).

**Recommendation 28 Opioid prescribing in patients with a history of addiction**
**The following are responsible for implementation of recommendation 28:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer and a history of substance misuse are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Methadone, buprenorphine and naltrexone are drugs used in the treatment of opioid addiction. Knowledge of their pharmacology and pharmacokinetics is important when managing cancer pain in patients with a history of substance misuse. Methadone may be used either as a treatment for addiction, or as an analgesic agent. | |
| **Key recommendations** | |
| **D** | **28.1** Communication with the patient's addiction services and primary care team should be maintained.<br><br>For patients on methadone maintenance therapy (MMT), when using opioids other than methadone for analgesia, the MMT should be continued. When using methadone as an analgesic, once daily dosing will be ineffective. |
| **D** | **28.2** Methadone should be used as an analgesic agent only under specialist supervision. |

### *2.3.6.6 Patients recovering from addiction*

Prolonged substance misuse may lead to changes in the neural reward circuitry, giving rise to the potential for relapse if opioids are required for analgesia. This is often a source of anxiety to patients, who may under report their symptoms, and healthcare professionals, who may under-treat pain (291). Relapse prevention theories show that the stress associated with unrelieved pain is more likely to trigger relapse than adequate analgesia in these patients (298). A plan for pain management in such patients should include a clear plan to taper opioids, as pain allows (291). **Level 5**

**Non-opioid interventions**
Adjuvant agents such as anti-convulsants and anti-depressants should be used where appropriate. Similarly, non-pharmacologic strategies such as nerve blocks should be utilised where possible (291, 294).

Focusing on pain as entirely organic and nociceptive in origin may lead to overuse of pharmacological interventions, underuse of other interventions and an increased risk of opioid-related toxicity (300). The impact of co-morbid psychiatric conditions should be taken into account in the management of pain, and measures such as brief counselling should be considered (294). **Level 4**

**Communication, goal setting and support**
Effort should be made to set realistic goals of treatment, and response to treatment should be regularly reviewed. The role of a contract between the physician, the treating multidisciplinary team and the patient has had anecdotal success. Advice should be sought at an early stage from a pain specialist or addiction psychiatry services, where appropriate (291). **Level 5**

**Recommendation 29 Opioid prescribing in patients recovering from addiction**
**The following are responsible for implementation of recommendation 29:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| Key recommendation | |
|---|---|
| **D** | For patients recovering from addiction, opioids should be tapered when their pain allows.<br><br>For all patients with a history of substance abuse, the use of adjuvant agents and non-pharmacological interventions should be maximised. |

## 2.4 Non-opioid pharmacological management

The World Health Organisation (WHO) cancer pain relief guidance (121) recommends the use of non-opioid and adjuvant analgesics in a stepwise manner (see section 2.2.9). Paracetamol and NSAIDs are considered to be the non-opioids of choice. An adjuvant analgesic is a drug which is not an analgesic in its prime function but, in combination with analgesia, can enhance pain control. Examples of adjuvant analgesics include antidepressants, anti-epileptics, corticosteroids and local anaesthetics. The evidence to support the use of non-opioid and adjuvant analgesics in the treatment of cancer pain is examined here.

### *2.4.1 Paracetamol*

Paracetamol is well established as an effective and well tolerated agent in the management of mild to moderate pain (301). When used alone, paracetamol has been shown to be more efficacious than placebo in the management of cancer pain (302). In addition, as an integral component of the WHO analgesic ladder, paracetamol is routinely used in cancer pain in combination with more potent analgesics. For example, codeine/paracetamol combinations have been identified as a useful option in the second step of the WHO analgesic ladder (146) (see section 2.2.10). **Level 1b**

- A prospective clinical study by Axelsson et al (2008) assessed the effect of withdrawing paracetamol from the analgesic regime of 34 cancer patients with well controlled pain on strong opioids (303). Of the patients evaluated, 68% felt no difference in pain levels with the cessation of paracetamol and only 18% wanted to continue taking it. The authors suggest that while their findings require verification, a critical evaluation in all patients of the subjective additive analgesic effect of paracetamol in concurrent strong opioid therapy is advisable. **Level 3**
- Mercadante et al performed a systematic review of the evidence for paracetamol in addition to strong opioids in 2013, and found no evidence to suggest that paracetamol confers an additional benefit over strong opioids, especially at doses less than 4g / day (304).
- Nabal et al (2012) performed a systematic review of the literature regarding the role of paracetamol and NSAIDs in addition to step III opioids (305). This was performed as part of the EPCRC guideline development process, but published following dissemination of the main guidelines. The review updated the 2005 Cochrane review, which had previously guided practice (302) Twelve studies were included in the review, of which seven investigated the role of NSAIDs and five investigated the role of paracetamol in addition to Step III opioids. **Level 1b**

Five double-blinded randomised controlled trials, three with cross-over design, examined the efficacy of various opioids used alone versus the efficacy of the same opioid in combination with paracetamol. Four studies, comprising a total of 166 patients, failed to confirm any benefit with the addition of paracetamol, and one study reported a small mean benefit.

- Israel et al (2010) performed a double-blind crossover trial, comprising 31 patients, and found that the addition of paracetamol to various opioids (at doses equivalent to or greater than 200mgs of morphine sulphate / day) did not provide any benefit in terms of analgesic efficacy or side effects (306). The authors suggest the cessation of paracetamol in patients on high dose opioids, and that paracetamol should not be added to step III opioids.
- Axelsson et al (2003) conducted a double-blinded crossover trial in 42 patients, comparing analgesic efficacy with paracetamol and morphine sulphate versus morphine alone, where the median oral daily dose of morphine sulphate was 70mg (range 20-440mg) (307). No additional analgesic benefit was demonstrated, but the effect on side-effects and opioid consumption was not reported.
- Tasmacioglu et al (2009) conducted a randomised double-blinded trial in 43 patients examining the effectiveness of intravenous paracetamol when added to morphine sulphate (308). No benefit was noted in terms of analgesic efficacy, side effects, or opioid consumption.
- Cubero et al (2010) compared the efficacy of methadone and paracetamol versus methadone alone in 50 patients with a double-blinded study with a follow-up duration of 7 days (309). No evidence of difference in analgesic efficacy was detected, but an increase in somnolence was noted in the patients who received paracetamol in addition to methadone.
- Stockler et al (2004) conducted a double-blinded crossover trial in 34 patients with advanced cancer who had pain despite strong opioids (median daily opioid dose equivalent to 200mg of oral morphine sulphate) (310). A slight benefit in terms of analgesic efficacy, of 0.4 on a 0 -10 numerical rating scale, was demonstrated with the addition of paracetamol. It was noted that this study used a higher than standard dose of paracetamol of 5g / day, and had a short follow-up duration of 96 hours.

Four studies did not report data regarding the effect of the addition of paracetamol on opioid consumption, and one study found no evidence of difference. Studies were small, with generally short follow-up durations. The weak evidence, if any, of the effectiveness of combining paracetamol with step III opioids, does not support the role of paracetamol in addition to step III opioids in patients with cancer pain (305).

**Level 1b**

In the absence of predictive factors to determine which patients will respond or not to paracetamol (303), it would seem prudent to continue to prescribe paracetamol in accordance with the WHO guidance (121), but to review its need in patients with well controlled pain on concurrent strong opioids.

**Recommendation 30 Paracetomol**
**The following are responsible for implementation of recommendation 30:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Paracetamol continues to have a role as an analgesic in patients with cancer pain, in accordance with the WHO analgesic guidance. | |
| **Key recommendations** | |
| **A** | **30.1** Paracetamol should be considered for patients with mild to moderate cancer pain, in accordance with the WHO Cancer Pain Relief guidance. |
| **A** | **30.2** There is insufficient evidence to support the addition of paracetamol for analgesic purposes in patients taking high doses of step 3 opioid medication in a cancer setting. |

### *2.4.2 Non-steroidal anti-inflammatory drugs (NSAIDs)*

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted as a treatment option for cancer pain. The WHO guidelines suggest an NSAID as a potential non-opioid for use at the first step of the WHO analgesic ladder, and throughout a patients escalating pain trajectory (121) (see section 2.2.10).

- McNichol Ewan at al (2005) performed a systematic Cochrane review to assess the effects of NSAIDs alone, or in combination with opioids, for the treatment of cancer pain (302). Forty two trials, involving 3084 patients were included. In relation to this review: **Level 1b**
  - Data from eight papers found NSAIDs to be more effective than placebo for cancer pain management.
  - Thirteen studies compared one NSAID with another. The review failed to identify any clear evidence to support the superior safety or efficacy of one NSAID over another, thus the selection of a particular NSAID was not conclusively established.
  - Twenty three trials investigated the effects of NSAIDs in combination with opioids; conflicting evidence was reported. While some studies disclosed no difference, others described a slight but statistically significant increase in pain relief compared to either drug alone; however, they do not necessarily demonstrate that this combination is synergistic. The possibility that increasing the dose of either single entity would achieve a similar outcome cannot be discounted.
  - The authors were unable to draw any firm conclusions regarding the association between dose, efficacy and safety. Conflicting results, along with short duration of studies, did not adequately address whether escalating doses increase pain reduction and/or increase the incidence and severity of side-effects. **Level 1b**

Nabal et al (2012) performed a systematic review of the evidence for NSAIDs in addition to strong opioids (305).

- The evidence for the efficacy of NSAIDs in addition to Step 3 opioids in cancer pain was reviewed. Seven studies, comprising a total of 196 patients, were identified, which compared NSAID / opioid combinations with opioid alone. Five studies demonstrated a benefit in terms of improved analgesia (three studies) and reduction in opioid consumption (two studies) when NSAIDs were added. **Level 1b**
  - Duarte-Souza et al (2007), in a double-blind crossover study including 34 patients, compared the analgesic efficacy of dipyrone in addition to morphine sulphate with morphine sulphate alone (311). It was shown that greater analgesic efficacy was achieved with the addition of the NSAID, but each phase lasted only 48 hours, and any potential carry-over effect between phases was not considered in the analysis.
  - Mercadante et al (2002) compared ketoralac 60mgs / day PO in addition to morphine sulphate with morphine sulphate alone, in 50 patients with a baseline pain intensity of less than 4 (NRS scale 0-10) (312). A reduction in opioid consumption was noted with the addition of the NSAID. More frequent constipation was noted in the opioid group, and more gastric discomfort in the NSAID group.
  - Bjorkman et al (1993) examined the effect of the addition of diclofenac 100mgs / day per rectum to intravenous morphine sulphate with a median daily dose of 105mgs / day, titrated to effect using patient-controlled analgesia before the addition of the NSAID (313). Average pain intensity reduction of 26% was not statistically significant, however daily morphine sulphate requirements reduced significantly from a mean of 95mg to 83 mg / day.
  - Two studies did not show any difference in analgesic efficacy with the addition of choline magnesium trisalicylate (314) and flurbiprofen (315) to opioid therapy alone.

  The studies were too heterogeneous in terms of specific NSAID used, dose, and follow-up duration, to perform a meta-analysis in terms of analgesic benefit, or to draw conclusions regarding NSAID side-effects. However, the weak evidence available indicates that NSAIDs can improve analgesia, or reduce opioid requirements, for patients with cancer pain in combination with Step III opioids (305). **Level 1b**

Although it is not feasible to recommend an optimal dose of NSAID based on the available evidence, advice from the Commission on Human Medicines (CHM) states that the lowest effective NSAID dose should be used for the shortest period to control symptoms, and the need for long term treatment should be reviewed regularly (316, 317). From a pharmacoeconomic perspective, in one prospective randomised controlled study carried out in 156 consecutive advanced cancer patients with pain, it was demonstrated that the use of NSAIDs in addition to strong opioids had a negligible impact on cost and reduced the need for further opioid dose escalation allowing for lower opioid dosing (312).

#### 2.4.2.1 Cardiovascular risk with NSAID use

Recent evidence has linked NSAID use to cardiovascular risk.

- Kearney et al (2006), in a meta-analysis of randomised trials, showed that COX-2 selective inhibitors demonstrate an increased risk of thrombotic cardiovascular adverse reactions, particularly myocardial infarction (MI) and stroke (318). **Level 1a**
- Following a comprehensive Europe-wide review of clinical trial and epidemiological data in 2006, the Commission on Human Medicines advised that non-selective NSAIDs may also be associated with a small increased risk of thrombotic events when used at high doses and for long term treatment (316). The findings from two more recent studies (319, 320) are consistent with, and hence validate, the earlier 2006 review. In addition, the newer studies reported an increased cardiovascular risk with all users of NSAIDs, irrespective of their baseline cardiovascular risk, and not only in chronic users. However, the greatest concern relates to chronic use of high doses (316). The risk is associated with selective COX-2 inhibitors, high dose diclofenac and high dose ibuprofen (>1200mg per day). Evidence indicates that naproxen is not associated with such a risk (316-318). **Level 1a**

#### 2.4.2.2 Renal toxicity with NSAID use

NSAIDs may provoke or worsen renal failure (see section 4). They should be used with caution in patients who are at high risk of developing renal impairment or those who are on concurrent potentially nephrotoxic drugs. Doses should be maintained as low as possible and renal function monitored as appropriate (19, 321).

#### 2.4.2.3 Gastrointestinal risk with NSAID use

Gastrointestinal (GI) complications are widely recognised as a commonly associated adverse effect of NSAIDs. The risk of GI toxicity with NSAIDs is increased by a number of factors including increasing age (>65 years), previous peptic ulcer disease and concurrent use of other drugs that may increase the risk of ulceration or bleeding (2).

- COX-2 selective inhibitors are associated with a lower risk of GI toxicity than traditional NSAIDs, however this advantage is diminished by the co-administration of low dose aspirin (322). **Level 5**
- Low dose ibuprofen (<1200mg per day) is associated with the lowest risk of GI complications compared to other traditional NSAIDs such as diclofenac and naproxen (316, 317). **Level 5**
- Rostom et al (2002) performed a systematic review to investigate strategies for the prevention of upper GI toxicity secondary to NSAIDs (323) and found evidence to demonstrate that double dose H2-antagonists and standard dose proton pump inhibitors (PPIs) are effective prophylactic agents. In high risk patients, a COX-2 inhibitor or a traditional NSAID plus a PPI appear to offer similar protection. While the authors surmise that the combination of a COX-2 inhibitor and a PPI appears to confer the greatest GI safety, there is no high quality evidence to support the use of such a combination (322, 324). **Level 1b**
- A systematic review and meta-analysis examining the benefits of COX-2 inhihibitors compared to the use of an NSAID + PPI combination found high quality evidence that COX-2 inhibitors reduce the risk of major gastrointestinal adverse events including bleeding and perforation in patients who are at high risk of such events, or requiring long-term therapy, while the use of an NSAID + PPI combination reduces the risk of dyspepsia (325). **Level 1a**

Risk stratification and identification of the individual cardiovascular and GI risk factors should inform the decision regarding choice of NSAID and gastroprotective

strategy (323, 326). In the absence of any GI risk factors, patients may be managed with a traditional NSAID. In the presence of GI risk factors, the choice can be made between traditional NSAID and a PPI, or a COX-2 inhibitor (324).

#### 2.4.2.4 NSAIDs: alternative routes of administration

**Subcutaneous**

Diclofenac is available in Ireland as an injection. Although only licensed for intravenous and intramuscular use, anecdotal evidence in the palliative care setting supports its routine use subcutaneously. It is typically given as a continuous subcutaneous infusion (CSCI) at a dose of up to 150mg/24 hours (148, 327).

**Level 5**

**Rectal**

Diclofenac is available as a suppository and can be administered in doses up to 150mg/day (given in divided doses) (148, 317).

**Recommendation 31 NSAIDS**

**The following are responsible for implementation of recommendation 31:**

*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding** | |
|---|---|
| Whilst non-steroidal anti-inflammatory drugs (NSAIDs) are effective for the treatment of cancer pain, there is no clear evidence to support the superior safety or efficacy of one particular NSAID over another.<br><br>In terms of choice of NSAID, there appears to be reduced cardiovascular risk for low dose ibuprofen (up to 1200mg/day) or naproxen. | |
| **Key recommendations** | |
| **A** | **31.1** NSAIDs should be considered for the treatment of cancer pain, both as single agents and in combination with step 3 opioids. |
| **D** | **31.2** Risk stratification and identification of the individual cardiovascular and gastrointestinal risk factors should inform the decision regarding choice of NSAID, and gastroprotective strategy. |
| **C** | **31.3** Patients taking NSAIDs who are at high risk of gastrointestinal complications should be prescribed either double dose H2-antagonists or a proton pump inhibitor as pharmacological prophylaxis. Patients in this category could also be considered for a COX-2 inhibitor, depending on their cardiovascular risk factor profile. |

### 2.4.3 Anti-depressants and anti-epileptics

Neuropathic pain mechanisms are present in up to 40% of patients with cancer pain (328). In order to achieve optimum pain control in these patients, it is often necessary to combine adjuvant analgesics, such as antidepressants and/or anti-epileptics, with standard opioid therapy. These medications may be associated with adverse effects. For example, neuropathic agents may cause cognitive disturbance, somnolence, nausea and dizziness (328, 329). Anticonvulsants may be associated with sedation, akathisia and anticholinergic side effects (330, 331).

#### 2.4.3.1 Evidence in cancer pain

- Bennett (2011) undertook a systematic review to evaluate the effectiveness of antidepressant and antiepileptic drugs when added to opioids, compared with opioid alone, for the management of pain caused directly by cancer (328). **Level 1b**
  - Eight studies comprising 465 patients were included in this review; five of these studies were RCTs and three were prospective before-after design studies. Six studies examined the anti-epileptics gabapentin, sodium valproate and phenytoin, while two studies examined the tricyclic antidepressants (TCAs), amitriptyline and imipramine.
  - Of the studies reviewed, two RCTs and two observational studies produced the strongest evidence. These supported the addition of gabapentin to patients taking opioids, as this showed a significant benefit when compared to an opioid alone.
  - The authors comment that in all adjuvants studied, the effect size was much less than that seen in patients with non-cancer associated neuropathic pain.
  - No studies evaluated the use of adjuvants commonly used in non-cancer neuropathic pain such as pregabalin or duloxetine. Therefore no comment could be made on their effectiveness in cancer associated neuropathic pain.
- Bennett concluded that the addition of an antidepressant or antiepileptic adjuvant to opioid therapy may improve outcomes in patients with neuropathic pain associated with cancer. Any benefits are likely to be apparent within 4-8 days, at which point dosage adjustment or a switch to an alternative adjuvant can be undertaken as necessary (328).
- Mishra et al (2012) performed a prospective randomized double-blind placebo-controlled trial of 120 cancer patients with severe neuropathic pain and compared the effect of amitriptyline, gabapentin, and pregabalin. They found there was statistically and clinically significant morphine sparing effect of pregabalin in relieving neuropathic cancer pain and neuropathic symptoms as compared to the other neuropathic drugs. This study did show some effectiveness of amitriptyline though significantly less than pregabalin (332). **Level 1b**

#### 2.4.3.2 Evidence in non-cancer pain

Evidence from studies in patient groups other than cancer has been reviewed, as some generalizability of results is considered possible. There is no direct evidence of comparative efficacy between different anti-epileptics or between anti-epileptics and antidepressants (2).

- An updated systematic Cochrane review of 61 randomised controlled trials (comprising 3293 patients) of 20 antidepressants was conducted by Saarto et al (2007) and provides robust evidence that antidepressants are effective in the management of neuropathic pain (333). No studies of serotonin and noradrenaline reuptake inhibitors (SNRIs) were included.
  - The best evidence for pain relief is for tricyclic antidepressants (TCAs), and amitriptyline in particular. **Level 1a**
  - Data from three studies suggests that venlafaxine at doses of 75mg – 225mg daily has similar efficacy to the TCAs.
  - There is limited evidence for the role of selective serotonin reuptake inhibitors (SSRIs), whose use may be restricted to those patients that experience relief from TCAs, but find adverse effects troublesome.
  - The evidence suggests that any therapeutic benefit is usually seen in a few days, if there is a response.

- The authors recognised that adverse effects with TCAs are well documented and can often be significant. Twenty percent of participants in the review withdrew as a result of intolerable side-effects of antidepressants.
- Based on this evidence, the authors recommend initiation with amitriptyline, with a switch to an alternative TCA or venlafaxine if some pain relief is achieved but side-effects are troublesome.

- Finnerup et al (2015) performed a systematic review and meta-analysis of the pharmacotherapy of neuropathic pain. This review only included neuropathic pain associated with nociceptive components (e.g. cancer pain) if the primary outcome of the study was related to neuropathic pain. 229 studies were included and trial outcomes were generally modest: in particular, combined NNTs were 6·4 (95% CI 5·2–8·4)for serotonin-noradrenaline reuptake inhibitors, mainly including duloxetine 7·7 (6·5–9·4) for pregabalin; and 7·2 (5·9–9·21) for gabapentin, including gabapentin extended release and enacarbil;. NNTs were lower for tricyclic antidepressants (3.6). However, the review highlights that there were few studies in cancer related pain (152).
- Lunn et al (2009) assessed the benefits and harms of duloxetine, an SNRI, for the treatment of painful neuropathy and different types of chronic pain, in a systematic Cochrane review (334). Six RCTs were evaluated, comprising 2220 participants. The authors concluded that there was moderately strong evidence that duloxetine 60mg and 120mg daily are efficacious for treating pain associated with diabetic peripheral neuropathy and fibromyalgia.

**Level 1a**

- Moore et al (2011) performed a Cochrane systematic review of 29 studies, comprising 3571 patients, to evaluate the use of gabapentin at doses of 1200mg or more in neuropathic pain (335). Two studies investigated its use in cancer-related neuropathic pain, in which there was no significant difference between gabapentin and placebo. Overall, gabapentin was found to provide a substantial benefit in 31% of patients and a moderately important benefit in 43% of patients with neuropathic pain.
- Moore et al (2009) conducted a Cochrane systematic review of 19 studies, including 7003 patients, to evaluate the efficacy of pregabalin in acute and chronic pain (336). The evidence suggests pregabalin, at doses of 300mg-600mg daily, is effective in the treatment of chronic neuropathic pain. Pregabalin 150mg daily was not found to be effective. The incidence of adverse effects, principally somnolence and dizziness increases with increasing dose. The authors recommend that individualisation of treatment is needed to maximise pain relief and minimise adverse events.
- WIffen et al (2011) performed a systematic Cochrane review of 15 studies, comprising 629 patients, to evaluate the analgesic efficacy of carbamazepine for acute and chronic pain management (337). Carbamazepine was found to be effective in the treatment of chronic neuropathic pain; however, trials were of short duration with small populations and inadequate outcomes reported. There is thus insufficient evidence available to support the use of carbamazepine as a first line treatment for neuropathic pain. The authors note that the need for monitoring and the potential for drug interactions has discouraged the use of carbamazepine in light of the emergence of newer anti-epileptics such as gabapentin and pregabalin.

**Recommendation 32 Antidepressants and anti-epileptics**
**The following are responsible for implementation of recommendation 32:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>There is evidence that antidepressants and anti-epileptics may improve cancer-related neuropathic pain.<br><br>There is evidence in the cancer setting to support the use of tricyclic antidepressants such as amitriptyline.<br><br>There is evidence in the non-cancer setting (which may be extrapolated to the treatment of cancer related neuropathic pain cancer setting) to support the use of serotonin-noradrenaline reuptake inhibitors such as venlafaxine, duloxetine.<br><br>There is insufficient evidence to support a recommendation on the use of selective serotonin reuptake inhibitors (SSRIs).<br><br>There is evidence in the cancer setting to support the use of anti-epileptics, such as pregabalin and gabapentin. | |
| **Key recommendation** | |
| **A** | In patients with cancer-related neuropathic pain, anti-epileptic and antidepressant medications should be considered, with careful monitoring of side effects. |

### *2.4.4 Bisphosphonates*

It is well recognised that there is a large body of evidence attesting to the beneficial effects of bisphosphonates in the prevention and treatment of skeletal-related events in cancer patients (2). Reducing the incidence of skeletal events undoubtedly contributes to the improvement of symptoms through the minimisation of bone pain and alleviation of disease burden. However, the focus of this section is restricted to evaluating the evidence base that describes the effects of bisphosphonates in reducing cancer pain.

- Evidence to support the role of bisphosphonates in the treatment of cancer pain associated with bone metastases is presented in a systematic Cochrane review by Wong et al (2002) (338). Thirty RCTs (3682 patients) were evaluated to determine the effectiveness of bisphosphonates for the relief of pain from bone metastases. The studies evaluated assessed the effects of etidronate, clodronate and pamidronate in a number of different primary disease sites including breast, prostate and multiple myeloma. The authors note that comparative analysis across studies was limited by variations in study design, patient population, pain assessment methods and pain related outcomes. They did, however, determine the following: **Level 1b**
  - There is evidence to suggest a significant benefit in favour of the use of bisphosphonates for pain relief. The magnitude of this benefit at 4 weeks is similar to that observed after 12 weeks; thus maximum response is likely to be observed at 4 weeks.
  - There was insufficient evidence to evaluate the comparative efficacy of the different bisphosphonates, the impact of the different routes of administration, or if there was any variation in analgesic response between different primary disease sites.

Wong et al concluded that there was insufficient evidence to recommend bisphosphonates for immediate effect as first line therapy, but that they should be considered where analgesics and radiotherapy have proven inadequate for the relief of painful bone metastases (338). **Level 1b**

The decade since the publication of the 2002 Cochrane review has seen the advent of a new generation of bisphosphonates, which have shown increased potency and tolerability. These newer generation drugs, zoledronic acid and ibandronate are now more commonly used in practice.

**Zoledronic acid**

The highly potent, third generation bisphosphonate zoledronic acid has demonstrated efficacy in reducing pain associated with bone metastases in a number of different tumour types, as follows:

- The efficacy of zoledronic acid in metastatic bone pain from breast cancer and multiple myeloma was compared to pamidronate in a phase III RCT of 1648 patients by Rosen et al (2001). Pain scores were reduced below baseline in the presence of stable or decreasing analgesic use, over a one year study period. There was no significant difference between the zoledronic acid and pamidronate treatment groups (339).
- The outcome of a placebo controlled trial of the efficacy of zoledronic acid in 643 men with prostate cancer conducted by Saad et al (2004) demonstrated significant and durable palliation of bone pain for patients treated with zoledronic acid compared with placebo. The authors report a clear dose response in the changes from baseline pain scores over the 24 month study period (340). **Level 1b**
- Kohno et al (2005) describe a consistent statistically significant decrease from baseline in composite pain scores compared with placebo throughout a 12 month study period in a RCT of 228 patients with breast cancer comparing zoledronic acid with placebo (341).
- A number of other studies have also reported significant reductions in pain and analgesic use in various primary malignancies over periods up to 12 months (342-344).

**Ibandronate**

Ibandronate, another potent third generation bisphosphonate, also has an established evidence base to substantiate the efficacy and safety of both oral and intravenous ibandronate formulations in the reduction of metastatic bone pain for up to 2 years (345-348).

- Body et al (2003) determined that intravenous ibandronate 6mg significantly improved pain scores compared with placebo in a randomised controlled trial of 466 women with breast cancer. Patients experienced a rapid decrease in initial pain scores that remained below baseline throughout the 2 year study period. This was reflected in a lower requirement for analgesia in the treatment group compared to placebo leading the investigators to conclude that the reduction in pain scores was not a result of increasing use of analgesics (345, 346). **Level 1b**
- Oral ibandronate significantly reduced bone pain scores from baseline compared with placebo in two randomised studies in patients with breast cancer (347, 348). The reduction below baseline was at almost maximum level within the first 8-12 weeks of treatment and maintained throughout the 96 week study period. Of note, analgesic use increased in all arms of these studies, although the mean increase was lower in the ibandronate group compared with placebo.

- Tolia et al performed a systematic review of the evidence in 2014, and found evidence to demonstrate that the bisphosphonates, including zoledronic acid and ibandronate, are effective in reducing pain and skeletal related events in breast, lung, thyroid, colorectal, and renal cancers, and in multiple myeloma (349). **Level 1b**

While the primary intent of bisphosphonate use is considered to be the reduction of skeletal-related events, clinical trials have established that these agents have an analgesic effect on patients with bone pain from a variety of tumours (350). There is a lack of randomised trial data to facilitate an evaluation of the comparative efficacy of bisphosphonates and their relative effects on bone pain; neither are there any formal comparisons to other analgesics or to radiotherapy (2, 350).

#### *2.4.4.1 Adverse effects*

The main adverse effects of bisphosphonates are renal toxicity, hypocalcaemia and osteonecrosis of the jaw (ONJ) (2, 19).

Reports of renal function deterioration associated with the use of bisphosphonates are well documented (351). Intravenous bisphosphonates are most nephrotoxic at higher doses, or following rapid administration. This is demonstrated by the improvement in renal adverse events following a dose reduction and increase in infusion time with zoledronic acid (345).

Clinical trial data suggests that IV ibandronate 6mg has a renal safety profile comparable with placebo over 2 years of treatment (345). There were no renal adverse events reported with loading dose of ibandronate in breast, prostate and other solid tumours (351). There is also evidence that oral ibandronate also has a comparable renal safety profile to placebo (348). While Body et al (2006) suggest that ibandronate has a more favourable renal safety profile than other bisphosphonates (345), comparative trial data is required to confirm this. **Level 1b**

The prevalence of ONJ in cancer patients receiving bisphosphonates is 6-10%. Published guidelines outlined the most significant predisposing factors as being the use of aminobisphosphonates, such as alendronate, risedronate and ibandronate, with an increasing risk over time of exposure and higher doses and a history of trauma, dental surgery or dental infection (2). Preventative strategies include treating all dental infection prior to commencement of treatment and avoiding invasive dental treatment when receiving IV bisphosphonates. The clinical judgment of the treating clinician should guide the management plan based on the individual risks/ benefits for the patient (2). **Level 5** **Level 5**

Calcium levels should be monitored during therapy with bisphosphonates as hypocalcaemia is a potential side effect. Calcium and vitamin D supplements may be considered if dietary intake is insufficient (2, 19).

#### *2.4.4.2 Denosumab*

Denosumab is a human monoclonal IgG2 antibody that targets and binds with a high affinity to human receptor activator of nuclear factor kappa-B ligand (RANKL). Its activity has recently been evaluated in a number of clinical trials, demonstrating its efficacy in reducing the incidence of skeletal-related events (SRE) (compared with zoledronic acid) in breast and other solid tumours and multiple myeloma (352-354). Pantano et al (2011) demonstrated that denosumab prevented clinically relevant

increases in pain compared with zoledronic acid across a variety of tumour types (breast, prostate, multiple myeloma and other solid tumours) and was similar to zoledronic acid in relieving pain (355).

With regard to the economic evaluation of denosumab, a health utility evaluation perfomed in 2013 (356) demonstrated that denosumab was effective in delaying time to first SRE and reducing the risk of multiple SREs compared with zoledronic acid, and that generally speaking, denosumab provided similar outcomes to zoledronic acid in terms of quality of life, pain, overall survival and safety. Cost-effectiveness analysis showed that in the absence of the patient access scheme (PAS, in the NHS UK), denosumab was not estimated to be cost-effective relative to either zoledronic acid or best supportive care. With the PAS, denosumab was estimated to be cost-effective relative to zoledronic acid but not best supportive care.

**Recommendation 33 Bisphosphonates**
**The following are responsible for implementation of recommendation 33:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Bisphosphonates are effective in reducing cancer pain associated with bone metastases.<br><br>Evidence demonstrates that zoledronic acid is effective in the reduction of cancer pain associated with bone metastases in a number of different tumour types, including breast, prostate, lung and multiple myeloma.<br><br>Evidence demonstrates that ibandronate is effective in the reduction of cancer pain associated with breast cancer and bone metastases. | |
| **Key recommendation** | |
| **A** | Bisphosphonates should be considered as part of a therapeutic regime for the treatment of cancer pain associated with bone metastases; however, there is insufficient evidence to recommend them as first line therapy. |

### *2.4.5 Corticosteroids*

The anti-inflammatory effects of corticosteroids have been reported to be useful in the management of cancer-related neuropathic and bone pain (19, 321, 357). Despite vast experience with corticosteroid use, there is a lack of robust evidence to support their role as an analgesic agent; much of the evidence is anecdotal, rather than based on prospective studies designed to assess analgesic effect or opioid sparing effect as a primary outcome. **Level 2a**

The role of corticosteroids in the context of pain treated by opioids is difficult to interpret. This is because corticosteroids may have contrasting effects on both pain and opioid response. While the well recognised anti-inflammatory effect may reduce the pain, recent research has suggested that activation of corticosteroid receptors in patients receiving opioids may negatively influence opioid analgesia (275). Steroids may also indirectly act to improve mood and sense of well-being, thus increasing pain tolerance and efficacy of any regimen (275).

A recent Cochrane review (Haywood et al 2015) assessed the role of corticosteroids in the management of cancer pain in adults. This review included 15 studies enrolling 1926 patients. Although some studies did convey some short term pain relief with the use of corticosteroids when compared to standard therapy, the overall result suggests a very weak positive effect at 7 days but with significant biases in evidence base. Longer trials (14 days) show no sustained effect and adverse effects were poorly documented (358). **Level 1a**

In 2014 a double-blinded randomized controlled trial of methylprednisolone versus placebo in patients with cancer-related pain (n = 47) found no effect on pain intensity at 7 days, although there were statistically and clinically significant improvements in fatigue, appetite, and patient satisfaction in the steroid group (359). **Level 1b**

Paulsen et al (2013) performed a systematic literature review to determine whether corticosteroids provide analgesic effects in cancer patients (357). The paucity of relevant studies was striking; consequently, the evidence was graded as ''very low''.

- The search provided 514 references, four of which were included. All studies involved patients with advanced malignancy.
- One crossover study showed a significant reduction in pain intensity of 13 (visual analogue 0-100 scale) accompanied by significant lower analgesic consumption in favour of the steroid group. In another study, the addition of steroids did not have any effect on pain. In two studies, outcomes of pain intensity or analgesic consumption were not adequately reported. However, one of these studies showed significant pain reduction, whereas the other found no effect. **Level 2a**
- The authors conclude that corticosteroids may have a moderate analgesic effect in cancer patients (357).

Mercadante et al (2007) evaluated the role of corticosteroids as adjuvants to opioid therapy in a prospective randomised study of 76 advanced cancer patients (275). The study showed no significant differences between the treatment groups, suggesting that corticosteroids do not contribute to analgesic improvement. The authors speculate that this may be a reflection of the low power of the study to detect so small an effect. Adverse effects associated with illness or induced by opioids were better tolerated in the steroid group, especially gastrointestinal symptoms. A short-lasting effect was observed on general symptom burden and sense of well-being. **Level 1b**

- The authors conclude that corticosteroids do not improve opioid analgesia or reduce opioid consumption in advanced cancer patients. However, the intensities of some opioid induced adverse effects, particularly gastrointestinal, seem to be relevantly and persistently lower, and a short lived improvement in general condition is expected.

There are no established dosing schedules for corticosteroids in cancer pain, however short term use of high doses followed by a rapid taper may be considered (360). **Level 5**

- Corticosteroids given in medium doses were well tolerated in studies for up to seven days. However, the studies indicated that corticosteroids may have serious toxicity and even higher mortality when administered in high doses over eight weeks (357). **Level 2a**
- Published guidelines have suggested a regimen of dexamethasone 8mg daily for 3-5 days until benefit is achieved, then reduction to the minimum effective dose (19). If no significant improvement is observed with 5 days, treatment should be discontinued. **Level 5**

Patients maintained on corticosteroids long term should be monitored for potential adverse effects, in particular proximal myopathy, Cushing's syndrome and steroid-induced diabetes.

**Recommendation 34 Corticosteroids**
**The following are responsible for implementation of recommendation 34:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>There is limited direct evidence regarding the role of corticosteroids in the management of cancer pain, and, on evidence to date, are unlikely to have an important role in cancer pain | |
| **Key recommendation** | |
| | Corticosteroids may have a **limited** role in the management of cancer-related pain, however there is insufficient evidence to allow a recommendation. |

### *2.4.6 Ketamine*

Ketamine is an NMDA (*N-methyl-D-aspartate*) receptor antagonist that is used to treat intractable pain that is unresponsive to opioid escalation and other agents. Its use is indicated in pain of varying aetiologies including neuropathic pain and refractory cancer pain (2, 301). It is usually administered as an adjuvant to strong opioids, producing a synergistic analgesic effect and reducing opioid tolerance (2, 361, 362).

Ketamine can be administered by multiple routes of administration including oral, intravenous, subcutaneous (363). As with all adjuvant analgesics, upon initiation of ketamine the dose of strong opioid may need to be reduced (2, 364). **Level 5**

The literature regarding use of ketamine in the cancer setting has been the source of considerable debate in recent years:

- The majority of the early published literature comprises case reports and case series. For example, Jackson et al (2001) described the use of short term "burst" of continuous subcutaneous infusion of ketamine, through an open label audit of 39 patients with cancer pain, and reported a beneficial effect (365). Additional case reports (362, 366) and studies (367) that describe the successful use of ketamine to treat refractory cancer pain have also been published. **Level 4**

- A systematic Cochrane review (368), updated in 2012, identified two small randomised controlled trials (369, 370) that suggested that ketamine improved the effectiveness of morphine sulphate in the treatment of cancer pain. However, the small number of patients (30 patients in total) and the heterogeneity of trials precluded pooling of data. The authors concluded that the evidence base was insufficient to make recommendations. The review was again updated in May 2012 (371) and while three new RCTs were identified for possible inclusion in the review, all three were excluded. Two studies were excluded because they involved group-sizes of fewer than 10 participants who completed the study (372-374) was not blinded and considered to be methodologically flawed (using morphine as control and morphine consumption as outcome measure). The authors again concluded that 'current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain. More RCTs are needed'. **Level 1b**
- Subsequently Hardy et al (2012) published a multisite, dose-escalation, double-blind, randomised, placebo-controlled trial, to determine whether ketamine is more effective than placebo when used in conjunction with opioids and standard adjuvant therapy in the management of chronic uncontrolled cancer pain (375).
    - The intervention was a subcutaneous infusion of placebo or ketamine (100mg, 300mg, 500mg) over 5 days. Ketamine would be considered of net benefit if it provided a clinically relevant improvement in pain (defined as a reduction in Brief Pain Inventory average score by >/=2 points from baseline in the absence of more than four breakthrough doses of analgesia over the previous 24 hours). 185 patients were included in the primary analysis; pain was of varying aetiology (mixed, somatic, visceral, neuropathic). Baseline pain scores were of moderate intensity with a BPI mean score 5.43 (range 2.47 to 8.08) in the intervention group, and mean 5.21 (range 2.37 to 7.64) in the placebo group).
    - The study failed to show additional clinical benefit for ketamine when delivered SC in a dose escalating regimen. A strong placebo effect was noted, and mean pain scores improved for all participants. There was a greater improvement in worst and average pain scores in the ketamine group for those patients with more severe pain, but this was found not to be clinically relevant (as defined above).
    - Psychotoxicity was more prevalent in the ketamine group by the study end (p=0.034), however the NNH was 6.

- Salas et al (2012) (373) also performed a randomized, double-blind, placebo-controlled study. Inclusion criteria were age 18 years, and cancer pain refractory to standard opiates. Evaluations were conducted at randomization (baseline), at ketamine or placebo introduction time (T0), and at 2 hours (T1), 24 hours (T2), and 48 hours (T3) after T0. The primary evaluation criterion was pain efficacy assessed using a patient self-rated Numeric Pain Intensity Scale (NPIS) at T1. The main secondary evaluation criteria were daily morphine dose, symptom evaluation (Edmonton Symptom Assessment Scale [ESAS]), and patient satisfaction (Pain Treatment Satisfaction Scale [PTSS]). **Level 1b**
  - The experimental group was given intravenous morphine and ketamine, while the control group was given intravenous morphine and placebo. Daily morphine dose could be increased daily by 50% if necessary. Morphine interdoses were planned with one-tenth of the daily dose. The interval between interdoses was fixed to one hour. The initial dosage was 0.5 mg/kg per day then 1 mg/kg per day after 24 hours if the NPIS score remained greater than or equal to 1.
  - Twenty patients were analyzed (11 received ketamine and 9 received placebo). Self-reported pain did not differ between the two groups, as the symptoms continued to evolve during the study period. The tolerance for ketamine was judged to be satisfactory.

The evidence from the controlled trials remains inadequate and contradictory to demonstrate effectiveness. Patient selection, dosing and use in palliative care is therefore still controversial, until further evidence becomes available. In summary, two initial small RCTs suggested that ketamine improved the effectiveness of morphine sulphate in the treatment of cancer pain. Two subsequent, larger RCTs found no evidence of benefit but have been criticized by some for patient selection and dosing.

With regard to the use of oral ketamine, the available evidence is in the non-cancer chronic pain population.

- Blonk et al (2010) conducted a review of 22 studies, comprising 166 patients, to evaluate the efficacy and safety of oral ketamine in chronic non cancer pain management (376). Sixteen of the studies were non-comparative observational studies or anecdotal reports, the remaining six were comparative studies, with only one RCT. The authors concluded the following:
  - Wide clinical use of ketamine is limited by psychotomimetic and other adverse effects. There were a high number of withdrawals due to such adverse effects. The duration of treatment was often limited as a result.
  - As an analgesic, ketamine has proven to be effective in patients with severe pain who have failed to respond to routine pharmacotherapy. Some patients who achieved good pain relief continued to take oral ketamine for several months. **Level 1b**
  - Efficacy and long term adverse effects are insufficiently studied to promote the routine use of oral ketamine in chronic pain management.

  The authors noted that the evidence for the effect of oral ketamine in chronic pain is limited and the quality of the studies is low. They conclude that oral ketamine may have a limited place as add-on therapy in complex chronic pain patients when other therapeutic options have failed.

Psychological disturbance and hallucination associated with ketamine may be minimised by administration of a benzodiazepine or an antipsychotic (364, 367). It has been suggested that the incidence of psychotomimetic side-effects increases in a dose dependent manner (365).

The use of ketamine should be initiated and supervised by a specialist in palliative medicine or pain management (2, 19).

**Recommendation 35 Ketamine**
**The following are responsible for implementation of recommendation 35:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Key finding** |
|---|
| There is conflicting evidence regarding the role of ketamine in the management of cancer pain.<br><br>There is some evidence supporting the use of oral ketamine in the refractory chronic non-cancer pain setting.<br><br>There is no evidence to guide which patients are most likely to benefit, or as to the optimal route of administration.<br><br>The use of ketamine should be initiated and supervised by a specialist in palliative medicine or pain management. |

| **Key recommendation** | |
|---|---|
| **D** | There is insufficient evidence to permit a recommendation to be made regarding the use of ketamine for the management of cancer pain. |

### *2.4.7 Lidocaine*

#### *2.4.7.1 Intravenous lidocaine*

The use of systemic local anaesthetic agents, such as lidocaine, as beneficial analgesics in neuropathic pain conditions has led to the consideration of its potential as an adjuvant analgesic in the treatment of opioid-refractory cancer pain. Although there is a lack of randomised controlled trial data to explore lidocaine's use, a number of retrospective reviews and case reports exist, both supporting and discounting its role, and generating conflicted opinion (377).

- Challapalli et al (2005) conducted a systematic Cochrane review of the use of systemic lidocaine and its analogues in neuropathic pain. Thirty controlled trials were evaluated, sixteen of which investigated the effects of intravenous lidocaine in 373 participants (378). However, only two of the trials investigated its use in cancer-related neuropathic pain.
  - A meta-analysis found intravenous lidocaine to be more effective than placebo, and as effective as other analgesics in decreasing neuropathic pain. **Level 1a**
  - Treatment with lidocaine was associated with significantly more adverse effects than placebo. No reports of severe toxicity or life threatening events were identified. In comparison with other analgesics used for neuropathic pain (morphine sulphate, gabapentin, amantadine, amitriptyline, ketamine or carbamazepine), no evidence was found to show that lidocaine was less safe or had more adverse effects. However, these results were limited by heterogeneity of the studies and inadequate information on this outcome. **Level 1b**
  - The authors concluded that lidocaine provides a clinically important analgesic effect that can relieve neuropathic pain in selected patients, compared with placebo.

- A retrospective chart review by Thomas et al (2004) assessed the clinical benefit of intravenous lidocaine in 82 inpatients in a hospice setting (379). The review produced preliminary evidence that parenteral lidocaine is well tolerated and rapidly effective for the acute management of opioid refractory pain, but recognised the need for more robust evidence in the form of RCTs. **Level 4**
- In 2009, a randomised controlled phase II pilot study was conducted by Sharma et al to evaluate the use of intravenous lidocaine in 50 patients with opioid-refractory cancer pain (377).
  - The trial demonstrated that a single infusion of lidocaine produced a significantly greater magnitude and duration of pain relief than placebo in opioid-refractory pain in cancer, with significantly more patients reporting a subjective decrease in analgesic requirements following lidocaine.
  - The mean duration of pain relief following a single infusion of 4mg/kg was found to be 9.34 days. The authors speculate that, as the duration of effect appears to last significantly beyond both the period of administration and the half-life of the drug, the prolonged duration of pain relief can be utilised to implement other more established treatment modalities. **Level 4**
  - The study was not powered to assess the safety profile of intravenous lidocaine; therefore no robust conclusions could be drawn. However, the side-effects experienced by 52% of the lidocaine population, were noted to be mild and self-limiting, and not significantly different from the placebo group.
  - The authors conclude that intravenous lidocaine may be a useful adjunct in the treatment of opioid-refractory cancer pain and may be considered as a temporary measure until further investigation establishes its role and safety profile.
- In contrast, two small controlled trials found no benefit of systemic lidocaine for the treatment of neuropathic cancer pain (380, 381). **Level 4**

Concern over the potential associated side-effects is perhaps one of the main arguments against the use of systemic lidocaine. It has been postulated that most side-effects are related to the rapid rate of infusion of high doses and the use of bolus doses. The adverse effects observed in studies have usually been of mild to moderate severity, the most common of which being somnolence or lethargy. Evidence to date has not generated reports of severe toxicity, cardiac or otherwise, that would necessitate withdrawal of treatment (377-379).

The use of intravenous lidocaine should be restricted to specialist settings (19, 382).

#### *2.4.7.2 Topical lidocaine*

The lidocaine 5% plaster is a medicated adhesive plaster, indicated for the relief of neuropathic pain associated with post herpetic neuralgia (PHN) (383). More recently, it is increasingly used for other painful neuropathic conditions. There is anecdotal evidence for use of lidocaine 5% plasters in cancer-induced bone pain, particularly vertebral metastases, which may have a neuropathic element (384). A maximum of three patches should be applied for 12 hours per day. Although there is minimal absorption, topical lidocaine should not be used in patients taking oral class I antiarrhythmic drugs. **Level 5**

Studies involving the use of the lidocaine plaster in a number of benign neuropathic conditions have shown it to be an effective and well tolerated topical analgesic (385). Two early RCTs (386, 387) in PHN demonstrated the plaster's superior pain relief when compared with placebo, a finding that has been confirmed in other neuropathic conditions (304, 388). To date, only one study has evaluated the lidocaine plaster in patients with cancer pain (389), and it failed to produce robust evidence in favour of its use.

**Level 1b**

- Finnerup et al, (2015) conducted a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies (152).
  - The target population was patients of any age with neuropathic pain according to the International Association for the Study of Pain definition (ie, pain caused by a lesion or disease of the somatosensory nervous system). Neuropathic pain associated with nociceptive components (eg, neuropathic cancer-related pain and radiculopathy) was included if the primary outcome of the study was related to neuropathic pain.
  - The authors used number needed to treat (NNT) for 50% pain relief as a primary measure and assessed publication bias; NNT was calculated with the fixed-effects Mantel-Haenszel method.
  - Based on the authors' inclusion criteria (trials of at least 3 weeks), they identified only one small negative study of 5% lidocaine patches in post-surgical neuropathic pain and two enriched-enrolment studies in post-herpetic neuralgia. The smaller study was positive; the larger study was negative in the intention-to-treat population, but positive in the per-protocol population. However, studies of shorter duration were positive, and safety and tolerability were good in all cases.
  - The authors conclude that lidocaine patches have a weak recommendation for use in neuropathic pain and are proposed as generally second line because of low effect sizes but high values or preferences and tolerability or safety. In some circumstances—eg, when there are concerns because of side-effects or safety of first-line treatments particularly in frail and elderly patients—lidocaine patches might be a first-line option.

**Level 1a**

To date, there has been extremely limited examination of use in the cancer setting:

- Fleming et al (2009) conducted a retrospective multi-centre audit of 97 patients with neuropathic pain within a cancer care setting (389). Only 18 of those patients had cancer-related neuropathic pain. Lidocaine 5% plaster was found to have a potent analgesic effect in 25% of patients, a partial effect in 24% and no analgesic effect or documentation of benefit in 47% of patients. Study methodology limits interpretation of findings (385). (Evidence level therefore not graded)
- Garzón-Rodríguez et al, (2013) performed a prospective, descriptive, non-controlled, nonrandomized, open-label study lidocaine 5 % patches as co-analgesic in patients with cancer pain secondary to painful scar or chest wall tumor (390). However, modification of the opioid dose was permitted during the follow-up period, as was anti-cancer treatment and interventional anaesthetic treatments, thus limiting interpretation of findings. (Evidence level therefore not graded)

**Recommendation 36 Lidocaine**
**The following are responsible for implementation of recommendation 36:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Intravenous lidocaine has been shown to provide analgesic benefit in the treatment of neuropathic pain in non-cancer patients.<br><br>Intravenous lidocaine may be a useful adjunct in the treatment of opioid-refractory cancer pain, though the evidence base is limited.<br><br>While there is evidence to support the use of lidocaine 5% plasters in post herpetic neuralgia and other benign neuropathic conditions, further studies are needed to fully elucidate its benefit in cancer pain. | |
| **Key recommendation** | |
| **D** | **36.1** Intravenous lidocaine may be a useful adjunct in the treatment of opioid-refractory cancer pain. Specialist advice should be sought if intravenous lidocaine is being considered. |
| **D** | **36.2** There is limited evidence to support the use of topical lidocaine plaster in cancer pain. |

### *2.4.8 Capsaicin*

Topical creams containing capsaicin are used to treat a wide variety of conditions, including neuropathic pain. Following application to the skin, the capsaicin causes enhanced sensitivity to noxious stimuli, followed by a period of reduced sensitivity and, after repeated applications, persistent desensitisation (391).

- Derry et al (2009) undertook a systematic Cochrane review to determine the efficacy and tolerability of topically applied capsaicin in chronic neuropathic pain (391). Six studies (389 participants) compared regular application of capsaicin 0.075% cream with placebo, while two studies (709 participants) compared a single application of a high dose capsaicin 8% patch with placebo.
  - The evidence suggests that capsaicin, either as a repeated application of low dose 0.075% cream or a single application of a high dose 8% patch, may provide some degree of pain relief in a range of neuropathic conditions, over a period of 6 to 12 weeks. **Level 1b**
  - Capsaicin was found to be commonly associated with localised skin reactions, which were often mild and transient, but that could lead to withdrawal of the patch.
  - The authors were unable to make robust estimates on the number of participants achieving clinically useful levels of pain relief, owing to limited data relating to different neuropathic conditions and inconsistent outcome definition (392).

- Finnerup et al, (2015) conducted a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies.
  - The target population was patients of any age with neuropathic pain according to the International Association for the Study of Pain definition (ie, pain caused by a lesion or disease of the somatosensory nervous system). Neuropathic pain associated with nociceptive components (eg, neuropathic cancer-related pain and radiculopathy) was included if the primary outcome of the study was related to neuropathic pain.
  - The authors used number needed to treat (NNT) for 50% pain relief as a primary measure and assessed publication bias; NNT was calculated with the fixed-effects Mantel-Haenszel method.
  - The results of five of seven studies (in patients with post-herpetic neuralgia or HIV-related painful polyneuropathy) showed sustained efficacy of a single application of high-concentration capsaicin patch (8%, better results for 60 min application in post-herpetic neuralgia and 30 min in HIV neuropathy) compared with a low-concentration patch (0.04%, to minimise the risk of unmasking related to the burning sensation of capsaicin).
  - The authors concluded that the final quality of evidence was high but effect size was small. Combined NNT was 10.6 (95% CI 7.4–18.8). Results for the secondary outcomes were inconsistent.
  - Therefore, the authors made a weak recommendation for use of capsaicin high-concentration patches as second line treatment for neuropathic pain (152).

**Level 1a**

The available evidence thus suggests that topical capsaicin may be useful as an add-on therapy for patients with painful neuropathic conditions with an inadequate response to, or intolerance of, other treatments (391). There is no evidence available examining the use of capsaicin in cancer pain.

**Recommendation 37 Capsaicin**
**The following are responsible for implementation of recommendation 37:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Limited available evidence suggests that capsaicin may be useful as an adjunctive treatment in the non-cancer setting. Studies are lacking in the cancer setting. | |
| **Key recommendation** | |
| | There is insufficient evidence to recommend the use of topical capsaicin for the treatment of cancer pain. It may provide some degree of relief in non-cancer related neuropathic pain conditions and could therefore be considered a worthwhile option as an adjunctive treatment. |

## 2.5 The use of opioids in patients with renal impairment

### 2.5.1 Renal impairment: classification

In recent years, the traditional classification of renal impairment into categories of mild, moderate and severe renal impairment has shifted towards a five-stage classification ranging from normal renal function to established renal failure, based on glomerular filtration rate (GFR). In the UK, the Chronic Kidney Disease eGuide (eCKD Guide, updated in 2009)(393) is widely utilised, and is derived from published national guidelines such as NICE (394), SIGN (2) and The Renal Association guidelines (395). Though not specifically designed for cancer patients, or for acute renal impairment, this classification is widely used and is applicable to the cancer population (179). It should be noted that:

- GFR or creatinine clearance (CrCl) measurements are superior to serum creatinine alone in assessing the degree of renal impairment.

The accuracy of formulae to derive estimated GFR (eGFR) or CrCl measurements is lessened in the presence of oedema, cachexia, low protein states and acute renal failure, all seen frequently in cancer patients.

**Table 13** Classification of Chronic Kidney Disease

| Stage | eGFR ml/min/1.73m$^2$ | Description |
|---|---|---|
| 1 | >90 | Normal kidney function. |
| 2 | 60-89 | Mildly reduced kidney function. |
| 3 | 30-59 | Moderately reduced kidney function. |
| 4 | 15-29 | Severely reduced kidney function. |
| 5 | <15, or on dialysis | Severe, or end-stage kidney failure. |

Modified from CKD eGUIDE, 2009 (393) and Palliative Adult Network Guidelines, 2011(19)
Note: eGFR should not be used for calculating drug doses in patients at extremes of body weight. Actual GFR is the more accurate guide to severity of renal failure.

### 2.5.2 Renal impairment in cancer

Declining kidney function is commonly seen in cancer patients due to disease, advancing age, reduced oral fluid intake and concomitant drug therapy (2). In such patients, medication side-effects can mimic the symptoms of opioid toxicity or terminal decline. Dehydration and renal impairment increase the potential for opioid toxicity or other drug side-effects by (19):

- Allowing the build-up of active drug metabolites
- Decreasing plasma protein binding capacity due to protein loss, or altered protein binding caused by uraemia
- Causing changes in hydration, affecting the distribution of drugs in the body
- Reducing oral absorption of drugs due to vomiting, diarrhoea and gastrointestinal oedema
- Increasing permeability of the blood brain barrier (in uraemia) which may exaggerate unwanted central nervous system side-effects.

King et al (2011) conducted a systematic review to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment and to produce guidelines (179). Fifteen original articles were identified, comprising eight prospective and seven retrospective clinical studies, but no randomised controlled trials. No results were found for codeine, dihydrocodeine, buprenorphine, tramadol or methadone. Overall evidence was found to be of very low quality. The authors concluded that the direct clinical evidence in cancer-related pain and renal impairment is insufficient to allow formulation of guidelines, but is suggestive of significant differences in risk between opioids

**Level 4**

The authors formulated a number of recommendations regarding opioid use in renal impairment and cancer pain, made on the basis of pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience. These recommendations have been adopted by the EPCRC and are referenced throughout this document.

### *2.5.3 Guidance for opioid prescribing in renal impairment*

In patients with poor or deteriorating kidney function, the following factors should be taken into consideration to prevent or manage toxicity (2):

- 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.

The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain when needed (179).

Dose adjustment recommendations should only be used as an initial guide, and further dose adjustments should be based on the clinical condition of the patient (2).

#### *2.5.3.1 Codeine*

Codeine is metabolised to morphine sulphate and its metabolites, which can accumulate in patients with renal impairment. Renal excretion of codeine and its metabolite codeine-6-glucuronide is reduced in patients with renal impairment (396); therefore caution with its use is required (396-398).

**Level 5**

- King et al (2011) did not find any studies that reported a clinical outcome relevant to the use of codeine in cancer-related pain and renal impairment (179).

#### *2.5.3.2 Tramadol*

Tramadol inhibits noradrenaline and serotonin uptake in addition to its weak opioid receptor activity. There is potential for serotonin-type side-effects and opioid adverse effects in patients with or without renal impairment. Tramadol is extensively metabolised in the liver to one active metabolite, O-demethyl tramadol (396). 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 (2).

**Level 5**

- King et al (2011) did not find any studies that reported a clinical outcome relevant to the use of tramadol in cancer-related pain and renal impairment (179).

### 2.5.3.3 Morphine sulphate

Morphine sulphate toxicity is well reported in patients with poor renal function (396-399) and is due to the accumulation of morphine sulphate-3-glucuronide (M3G) and morphine sulphate-6-glucuronide (M6G) (400). Morphine sulphate is metabolised primarily in the liver and the metabolites are largely excreted by the kidneys.

Dose reductions and decreased frequency of administration should be considered depending on the degree of renal impairment (396). Toxicity caused by the accumulation of metabolites in cerebrospinal fluid can take several days to resolve after morphine sulphate is discontinued (398). **Level 5**

- The systematic review performed by King et al (2011) found evidence relating to the use of morphine sulphate in renal failure, including five prospective studies and two retrospective reviews.
  - Wood et al (1998) published a study of 36 hospice inpatients taking morphine sulphate (401). Serum creatinine levels were significantly higher in the group with side-effects, as were M3G and M6G levels. All of the patients with elevated serum creatinine levels had nausea and vomiting, or delirium. **Level 4**
  - A prospective study by Tiseo et al (1995) did not show any significant association between renal function and morphine sulphate toxicity in nine critical adverse effects (402). The authors did note an association between creatinine levels and side-effects. **Level 3**
  - Somogyi et al (1993) found no significant relationship between metabolite (M3G and M6G) to morphine sulphate ratios, and serum creatinine concentration in eleven cancer patients receiving morphine sulphate (403). There was also no evidence of a relationship between morphine sulphate, metabolite levels and pain scores. **Level 4**
  - Klepstad et al (2003) describe a prospective observational study of 298 cancer patients aimed at determining if routine measurement of serum concentration of morphine sulphate and its metabolites could predict clinical outcomes (404). They found no clear correlation between morphine sulphate, M3G and M6G concentrations and pain intensity, or treatment failure. **Level 2b**
  - Riley et al (2004) investigated possible factors that might predict a need to switch opioids, and failed to show any evidence of renal function as a risk factor (405). The study excluded patients with a creatinine concentration of 1.5 times normal, yet the absence of an apparent effect at mildly or moderately reduced GFR has potential significance (257). **Level 3**

King et al (2011) state that the evidence relating morphine sulphate metabolite concentrations to clinical effects in patients with renal impairment is conflicting, but conclude that morphine sulphate is associated with an increased risk of adverse effects in patients with renal impairment (179). **Level 4**

### 2.5.3.4 Oxycodone

Oxymorphone and noroxycodone, the principal metabolites of oxycodone, are excreted renally. The contribution of these metabolites to the pharmacological activity of oxycodone is uncertain, but thought to be small (2, 398). Reduced excretion of oxycodone in renal impairment has been reported (396). **Level 5**

- King et al (2011) reviewed the limited evidence available:
  - A small prospective observational dose titration by Narabayashi et al (2008)(267) found that patients who had difficulty using morphine sulphate achieved 'high adequate pain control' when treatment was switched to oxycodone. **Level 4**

- Case reports of toxicity in association with oxycodone use in renal impairment exist (179). **Level 4**

The authors conclude that oxycodone should be used with care in patients with renal impairment. In severe renal impairment (eGFR<30 ml/min/1.73m$^2$) start with small doses and slowly titrate. **Level 2a**

#### *2.5.3.5 Hydromorphone*

Hydromorphone is metabolised in the liver, principally to hydromorphone-3-glucuronide. All metabolites are excreted renally (398).

- King et al (2011) reviewed the limited evidence available:
  - Lee et al (2001) compared the efficacy and outcomes of switching from another opioid to hydromorphone in 26 patients with normal renal function and 29 patients with renal impairment. The study included inpatients in a palliative care unit, most of whom had cancer (406). After the switch, over 80% of patients showed an improvement in side-effect profile. Hydromorphone was found to be safe and effective in patients with renal impairment.
  - Clemens et al (2009) evaluated 140 patients with renal failure, the majority of whom were taking morphine sulphate, and found evidence to suggest that a change to hydromorphone resulted in greater analgesia and reduced adverse effects (407). **Level 4**
  - Some published case reports have described hydromorphone toxicity in patients with renal failure, and there is evidence from a single case report of accumulation of hydromorphone-3-glucuronide in chronic renal failure (408).

Evidence for the safety of hydromorphone in renal impairment is inconsistent. However, hydromorphone is used in many units that deal with renal impairment frequently, and there are many reports of its successful use in such patients, when titrated carefully (179). **Level 4**

#### *2.5.3.6 Fentanyl*

Fentanyl is metabolised in the liver to compounds thought to be inactive and non-toxic, with less than 10% excreted unchanged in urine (396). Some reviews have reported studies concluding that no dose adjustment is needed in patients with renal impairment (396, 397). However, an increased elimination half-life has been reported in critically ill patients with renal failure (396). It would be prudent to monitor patients with renal failure for signs of gradual accumulation of fentanyl and its metabolites (398). **Level 5**

- King et al (2011) found limited evidence for the use of fentanyl in renal failure.
  - A retrospective review by Mazzacato et al (2006) (409) described 53 patients in a palliative care unit with renal impairment, all of whom were treated with subcutaneous fentanyl. Pain control was complete or partial in 85% of patients. In patients with opioid-related neurotoxicity, an improvement in pain was seen in 57% of patients. **Level 4**
  - There are case reports of the successful use of fentanyl in patients with renal failure, and it is used as a first-line opioid in patients with renal failure in many centres. **Level 5**

#### *2.5.3.7 Alfentanil*

Alfentanil is a synthetic derivative of fentanyl. It is less potent than fentanyl and is metabolised in the liver, with urinary excretion of the metabolites (which are thought to be inactive) (148, 179).

- King et al (2011) discussed the following studies;
  - Kirkham and Pugh (1995) described a retrospective series of four patients with impaired renal function who were agitated on a continuous subcutaneous infusion (CSCI) of diamorphine sulphate. Adverse symptoms improved in all four cases on rotation to alfentanil (410).
  - Urch et al (2004) retrospectively reviewed alfentanil use in a hospital palliative care setting (411). Of 81 patients on alfentanil, 41 patients had renal impairment. Alfentanil was routinely used as an alternative to morphine sulphate if serum creatinine was over 105 mmol/l. Approximately half of the patients who were subsequently converted back to alternate oral opioids developed opioid toxicity within 48 hours. **Level 4**
  - Alfentanil is used as an opioid of second choice for renal patients in some centres. **Level 5**

The authors conclude that the evidence for the safe use of alfentanil in patients with renal impairment is limited to retrospective reports of adequate analgesia and improved symptoms in patients switched from other opioids due to poor tolerability (179). **Level 4**

#### *2.5.3.8 Buprenorphine*

Buprenorphine is metabolised mainly to norbuprenorphine, which is the only metabolite thought to have analgesic activity (397). Unchanged buprenorphine is mainly excreted in the faeces and its metabolites are mainly excreted in the urine.

- King et al (2011) in their systematic review did not find any studies that reported a clinical outcome relevant to the use of buprenorphine in cancer-related pain and renal impairment (179). **Level 4**
- In 2014 Melilli et al (412) carried out a small prospective parallel-group active-controlled study (n=42) that evaluated the efficacy, safety and tolerability of transdermal buprenorphine for moderate/severe pain control in patients with cancer and renal function impairment (serum creatinine level ≥ 1.3mg/dL[115 micromol/L]) compared with use of of transdermal fentanyl in patients with cancer pain without renal impairment (serum creatinine ≤ 1.2mg/dL [106 micromol/L]). There were no significant differences in pain scores between the groups and the adverse effects reported did not show significant association with the study groups. The authors concluded therefore that in patients with cancer and renal impairment, transdermal buprenorphine is as safe and effective for moderate/severe pain control as transdermal fentanyl in patients with cancer without renal impairment, although the study was limited by the relatively small sample size and lack of accurate measurement of renal function (412). **Level 4**

Buprenorphine is considered generally safe to use in renal impairment as its pharmacokinetics are largely unchanged (396). However, there remains relatively little experience with this drug in cancer pain (179, 397). **Level 5**

#### 2.5.3.9 Methadone

Methadone is primarily excreted in the faeces, with approximately 20% excreted unchanged in urine. Methadone tends to accumulate in tissues with chronic use, has a long half-life and is highly protein bound (19). These factors make methadone use for analgesia potentially complex, even in the absence of renal failure. Due to its long half-life, methadone should be dose reduced in renal impairment. It is recommended that methadone should only be used under experienced specialist supervision because of the risks of accumulation and toxicity (179). **Level 5**

- King et al (2011) did not find any studies that reported a clinical outcome relevant to the use of methadone in cancer-related pain and renal impairment (179). **Level 4**

### 2.5.4 Opioid metabolites in patients with renal impairment

Given that the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment is low, any recommendations made must do so on the basis of pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience (179). The evidence however is suggestive of significant differences in risk between opioids, as summarised in Table 14.

**Table 14** Risk stratification of opioids

| Drug | Recommendations in patients with cancer and renal impairment | Comment |
|---|---|---|
| Codeine | If judged appropriate to use, then do so with caution. | Metabolised to morphine sulphate and codeine-6-glucoronide, which accumulate in renal impairment. No clinical studies of use in cancer pain and renal impairment (RI) identified. However, there have been reports of severe hypotension, respiratory arrest and profound narcolepsy in patients with advanced RI in the general population (413). The manufacturer advises that codeine is used cautiously, at a reduced dose, in patients with RI and avoided in patients with severe RI (414). However, codeine is used in practice in some renal units (415). |
| Tramadol | If judged appropriate to use, then do so with caution. | Metabolised extensively in the liver. Unmetabolised tramadol and its metabolites may accumulate in RI. No clinical studies identified in cancer pain and RI population but expert opinion suggests that when using weak opioids, tramadol should be used in preference to codeine. The manufacturer recommends that the dosage interval should be increased to 12 hours if CrCl is less than 30ml/min (416). Modified release preparations should be avoided (413). In severe RI (CrCl <10ml/min), tramadol is not recommended due to prolonged elimination (416). |
| Morphine sulphate | If judged appropriate to use, then do so with caution. | Active metabolites produced via hepatic metabolism (morphine-3-glucoronide and morphine-6-glucoronide) accumulate in renal impairment. Studies demonstrate an increased risk of adverse events in renal impairment. |
| Oxycodone | If judged appropriate to use, then do so with caution. | Metabolised to oxymorphone and noroxycodone in liver. Excreted renally. Inconsistent evidence regarding safety in renal impairment. The manufacturer contraindicates its use in severe RI (CrCl <10ml/min) (417). |
| Hydromorphone | If judged appropriate to use, then do so with caution. | Metabolised in the liver to hydromorphone-3-glucoronide. All metabolites excreted renally.<br><br>Evidence for the safety of hydromorphone in renal impairment is inconsistent. However, hydromorphone is used in a number of units that deal with renal impairment frequently, and there are reports of its successful use in such patients, when titrated carefully. |
| Fentanyl | May be used in renal impairment. Opioid of choice, along with alfentanil, in severe RI | Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight. |
| Alfentanil | May be used in renal impairment. Opioid of choice, along with fentanyl, in severe RI | Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight. |
| Buprenorphine | If judged appropriate to use, then do so with caution. | Metabolised to norbuprenorphine and norbuprenorphine-3-glucuronide, which are excreted in the urine; unchanged buprenorphine is mainly excreted in the faeces. Limited amount of evidence for use in RI in general population (413) and cancer population (412). The manufacturers of the buprenorphine patch suggest no dose changes are required (417) whereas RI is listed as a precaution for the 2mg sublingual tablets (419). |
| Methadone | If judged appropriate to use, then do so with caution in the specialist setting only | Primarily excreted in the faeces, with 20% excreted unchanged in the urine. No clinical studies identified and pharmacology is complex. |

### *2.5.5 Dosage recommendations*

#### *2.5.5.1 Mild to moderate renal impairment (179)*

Estimated glomerular filtration rate (eGFR) 30–89ml/min/1.73m$^2$ (mild to moderate renal impairment)

- All opioids that are appropriate for cancer pain can be used, with consideration of reduced dose or frequency at lower eGFR levels.
- Monitor for changes in renal function and consider a pre-emptive change of opioid in rapidly deteriorating renal function.
- Assess for any reversible factors.
- Be aware that estimations of GFR may be less accurate in the presence of cachexia, low protein states, oedema and with acute renal failure. An estimated GFR at the lower end of the moderate renal impairment range should therefore prompt consideration of a change of opioid to one considered safer in renal impairment.

#### *2.5.5.2 Severe and end stage renal impairment (179)*

Estimated glomerular filtration rate (eGFR) <30ml/min/1.73m$^2$ (end-stage renal failure and severe renal impairment).

- Due to the delay in the onset and offset of action, the transdermal route should be avoided if stable pain control has not been achieved. Even with stable pain control, careful consideration is needed due to the potential for delayed toxicity.
- Methadone may be useful if used by those experienced in its use for pain management.
- Remifentanil needs further assessment as to their suitability for use in cancer pain and renal impairment.
- If fentanyl or alfentanil is not available, alternative opioids may be used at reduced doses and frequency of administration, and with careful monitoring. If it is not appropriate or practical to use injectable, buccal, sublingual or nasal preparations for PRN use, then alternative opioids may need to be used (at reduced doses and frequencies). However this is likely to represent a risk of toxicity.

**Table 15** Dosage recommendations
(Adapted From Renal Drug Database for opioids in patients with renal impairment (420) and UK Medicines Information)(415)

| Opioid | GFR |
|---|---|
| **Codeine** | • 20-50ml/min: dose as in normal renal function<br>• 10-20ml/min: 30mg up to every 4 hours. Increase if tolerated<br>• < 10ml/min: 30mg up to every 6 hours. Increase if tolerated |
| **Tramadol** | • 20-50ml/min: Dose as in normal renal function<br>• 10-20ml/min: 50-100mg every 8 hours initially and titrate dose as tolerated<br>• <10ml/min: 50mg every 8 hours initially and titrate dose as tolerated |
| **Morphine** | • 20-50ml/min: 75% of normal dose<br>• 10-20ml/min: Use small doses (50% of dose), eg. 2.5-5mg and extended dosing intervals. Titrate according to response<br>• <10ml/min: Use small doses. Eg.1.25-2.5mg and extended dosing intervals. Titrate according to the response<br><br>Avoid slow release oral preparations as any side effects may be prolonged |
| **Oxycodone** | • 20-50ml/min: Start with 75% of dose. Dose as in normal renal function<br>• 10-20ml/min: Start with 75% of dose. Dose as in normal renal function<br>• <10ml/min: Start with small doses e.g. 50% of dose<br><br>Has been used in CKD 5 patients; start with lowest dose and gradually increase dose according to response. |
| **Hydromorphone** | • 20-50ml/min: Dose as in normal renal function<br>• <10-20ml/min: Reduce dose – start with lowest dose and titrate according to response |
| **Fentanyl** | • 20-50ml/min: 75% of normal dose. Titrate according to response<br>• 10-20ml/min: 75% of normal dose. Titrate according to response<br>• <10ml/min: 50% of normal dose. Titrate according to response |
| **Alfentanil** | • <10-50ml/min: Dose as in normal renal function |
| **Buprenorphine** | Transdermal: Dose as in normal renal function |
| **Methadone** | • 10-50ml/min: Dose as in normal renal function<br>• <10ml/min: 50-75% of normal dose, and titrate according to response |

### 2.5.6 Non-opioid analgesics in renal failure

Paracetamol is metabolised by the liver with only 2-5% excreted unchanged in the urine and does not require dose adjustment in chronic kidney disease (421). It is considered the non-opioid analgesic of choice for mild-to-moderate pain in chronic kidney disease patients (182, 421). It has been suggested that an increase in the dose interval of paracetamol from every six to every eight hours when eGFR<10ml/min/1.73m$^2$ may be appropriate (182).

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause irreversible reduction in GFR, sodium and water retention aggravating hypertension, gastro-intestinal bleeding and hyperkalaemia (421). The Renal Drug Handbook (422) states that the inhibition of renal prostaglandin synthesis by NSAIDs may interfere with renal function, especially in the presence of existing renal disease.

- For selected patients, the potential risk of precipitating renal failure should be weighed against the benefits of improved pain control through the use of NSAIDs. This may be of particular consideration where prognosis is expected to be short.
- If using an NSAID, the patient's urea, creatinine and electrolytes should be monitored (422).

Adjuvant analgesics may also require dose adjustment in patients with renal impairment.

### 2.5.7 The use of opioids in patients receiving dialysis

The use of opioids in patients undergoing dialysis is a complex issue. The type of dialysis and whether an opioid and its metabolites are dialyzable needs to be taken into consideration (179, 422). The evidence base for the use of opioids in patients receiving dialysis has not been systematically reviewed, but King et al (2011) do provide some guidance based on clinical experience and a non-formalised review of available evidence (179). Beyond this, the evidence base consists largely of case reports and clinical experience.

Clinical practice varies amongst nephrologists and specialist advice should be sought. Specialist reference sources such as The Renal Drug Handbook or Renal Drug Database are useful resources (420, 422). Factors such as the need for additional analgesia around the time of dialysis should be considered. Regular and close monitoring is required when dose adjustments are made to the patient's opioid.

**Level 5**

**Recommendation 38 Opioids in renal impairment**
**The following are responsible for implementation of recommendation 38:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>The quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment is low.<br><br>The available evidence is suggestive of significant differences between the activities of opioid metabolites and therefore their relative risk profiles in patients with impaired renal function. | |
| **Key recommendation** | |
| C | In renal impairment, all opioids should be used with caution, and with consideration of reduced doses and/or frequency of administration.<br><br>Specialist advice should be sought when prescribing opioids in moderate to severe renal impairment.<br><br>The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain, when needed.<br><br>Close monitoring of pain and for signs of opioid toxicity is required.<br><br>Alfentanil and fentanyl are the safest opioids of choice in patients with stages 4 or 5 kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 $m^2$).<br><br>Paracetamol is considered the non-opioid analgesic of choice for mild-to-moderate pain in patients with renal impairment.<br><br>Adjuvant analgesics may require dose adjustment in patients with renal impairment. |

## 2.6 The use of opioids in patients with hepatic impairment

Liver disease covers a broad spectrum of conditions, from mild and self-limiting to severe with high mortality (423). For the purposes of this section the terms liver disease and hepatic impairment have been used interchangeably. The terms mild, moderate and severe liver impairment are used to describe the degree of hepatic dysfunction. However, there is lack of information to support the definition of these terms.

### *2.6.1 Aetiology*

Liver disease has multiple aetiologies (19, 424) and pain management in this patient population can be complex (19). Liver function can be altered as a result of malignancy either;

- Directly due to either primary liver cancer (usually hepatocellular carcinoma or cholangiocarcinoma) or secondary metastatic disease depositing within the substance of the liver (37)
- Indirectly due to local malignancy invading the liver by direct infiltration or as a result of backward pressure through blockade of blood vessels or the bile duct (37).

### 2.6.2 Opioid metabolism and use in hepatic impairment

The liver plays a pivotal role in the biotransformation of most opioids. The pharmacodynamic effects of these drugs may be affected in patients with liver impairment (37). The enzymatic system of the liver is central to opioid metabolism and clearance (37). Other factors such as hepatic blood flow, plasma protein binding and the presence of a porto-systemic shunt may also have a significant effect (37). Predicting impaired drug clearance can be difficult as there is no biochemical marker or formula that can accurately do so (19, 425). The presence of altered liver function tests in conjunction with the clinical presence of hepatic decompensation, such as the presence of jaundice, ascites, or encephalopathy, may alert the prescriber to the potential for altered drug metabolism (19, 222). The Child–Pugh score and the Model for End-Stage Liver Disease (MELD) can be used to assess the severity of hepatic dysfunction; however, these only offer a rough guide and cannot be used specifically to predict the ability of the liver to metabolise opioids (37).

There is a lack of reliable information on the behaviour of commonly used palliative care medicines in patients with liver disease (19). Consequently, advice regarding drug treatment should be patient specific (19). In general, the therapeutic index of any opioid is narrower in cirrhosis or liver disease than in healthy individuals (426). In these patients, opioids should be initiated at lower doses and titrated slowly using extended dosing intervals (426). Furthermore, ascites provides a reservoir (third space) for hydrophilic opioids (morphine sulphate, oxycodone, hydromorphone) which delays their clearance (426).

#### 2.6.2.1 Codeine

The data available on the use of codeine in liver disease is limited (37). The analgesic activity of codeine is primarily achieved through its metabolism to morphine sulphate by the hepatic enzyme CYP2D6 (426). The activity of this enzyme is reduced in advanced liver disease, resulting in a reduced rate of conversion of codeine to morphine sulphate. This may be the reason for its reduced analgesic activity in these patients.

#### 2.6.2.2 Tramadol

In moderate liver disease, the level of tramadol's active opioid metabolite (O-desmethyl tramadol) is reduced and its duration of action is prolonged (426). In severe liver disease, tramadol's bioavailability increases and its half-life can be as long as 13-22 hours (426). The half-life of sustained release tramadol can be even longer. The use of tramadol should therefore be avoided in hepatic failure and advanced cirrhosis (426). **Level 5**

- Kotb et al (2008) studied the pharmacokinetic profile of oral tramadol (50 mg) capsule in 20 patients with liver carcinoma compared with 10 healthy controls. Of the 20 patients with malignancy, 10 had primary hepatocellular carcinoma on a background of chronic hepatitis C and 10 had metastatic liver disease from another primary source (427). Plasma tramadol concentrations were measured in venous samples at intervals up to 12 hours by high-pressure liquid chromatography. This study found that tramadol's bioavailability was increased in patients with primary or secondary liver cancer, when compared to that of the control group (98%, 75% and 68%, respectively). Consequently, a recommendation was made to lengthen the dosage interval of oral tramadol, if it is to be used in patients with liver cancer for analgesic purposes, to 50 mg every 12 hours (427). **Level 4**

#### 2.6.2.3 Morphine sulphate

Advanced liver disease is associated with an increase in the oral bioavailability of morphine sulphate of up to 200% (37). This can lead to an increase in plasma levels and possible accumulation (37). A prolonged duration of action can be seen in association with a prolonged prothrombin time, hypoalbuminaemia, encephalopathy, ascites and jaundice (426). Oral bioavailability increases in cirrhosis due to reduced first pass metabolism (426). A possible increased bioavailability in early liver disease means that lower doses should be used with initial dosing, but at usual dosage intervals (426).

- Hasselstrom et al (1990) investigated the oral and intravenous kinetics of morphine sulphate in seven cirrhotic patients with a history of encephalopathy (428). This study found a significantly lower plasma clearance, a longer elimination half-life and a higher oral bioavailability of morphine sulphate in cirrhotic patients compared with a group of patients with normal hepatic function (428).
- Kobt et al (1997) found that the mean elimination half-life of morphine sulphate in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine sulphate preparation, and peak serum concentrations were almost three times as high (428). Patients with cirrhosis had a greater degree of sedation, but none developed encephalopathy (429). It was recommended that the dose for modified-release preparations should be reduced and that they be given less often when patients have cirrhosis (429). **Level 4**
- Mazoit et al (1987) conducted a study using a highly specific radioimmunoassay to measure unchanged morphine sulphate in plasma in six normal subjects and in eight cirrhotic patients with hypoalbuminemia, hyperbilirubinemia and prolonged prothrombin time (430). They concluded that in clinical practice, cirrhotic patients should have their dosing interval with morphine sulphate increased by about 1.5-fold to two fold in order to avoid accumulation and deleterious effects (430).

#### 2.6.2.4 Oxycodone

The liver has a significant role in the metabolism of oxycodone (431). Oxycodone is extensively metabolised by the CYP2D6 enzyme in the liver to noroxycodone, oxymorphone and their glucuronides. As such, the clearance of oxycodone is decreased in hepatic failure (431). In advanced liver disease, immediate release oxycodone has a prolonged half-life which is similar to that of sustained-release oxycodone in healthy individuals (426).

- Tallgren et al (1997) studied the pharmacokinetics and ventilatory effects of oxycodone in six volunteer patients with end-stage liver cirrhosis, before and after liver transplantation. The study found that the pharmacokinetics of oxycodone were clearly altered in these patients (431), its plasma clearance significantly reduced, and elimination half-life prolonged in all but one of the patients prior to–transplantation. However, after successful liver transplantation the pharmacokinetics of oxycodone were similar to those reported in healthy adults. **Level 4**

The manufacturers of oxycodone recommend that in a setting of hepatic impairment, controlled release oxycodone should be initiated at 1/3 to 1/2 of normal starting dose with subsequent slow and careful dose titration.

#### 2.6.2.5 Hydromorphone

Hydromorphone has a greater bioavailability in patients with cirrhosis, with reduced first-pass clearance but no increase in the half-life (426). Hydromorphone should be initiated at a lower dose in patients with moderate hepatic impairment, as it is primarily metabolised by the liver and thus increased opioid exposure may occur in patients with moderate hepatic impairment (426). Based on this information, it may be deduced that dosage intervals do not have to be significantly extended except in late-stage cirrhosis and overt hepatic failure (426).

- Durnin et al (2001) conducted an open, parallel-group, single dose study of oral immediate release hydromorphone in 24 Caucasian volunteers, 12 with normal hepatic function and 12 with moderate hepatic function (432). The authors concluded that the effect of moderate hepatic impairment on the pharmacokinetics of hydromorphone is to increase the bioavailability of the drug. Therefore, patients with moderate hepatic insufficiency should be started on a reduced dose and closely monitored during titration (432). **Level 4**

#### 2.6.2.6 Fentanyl

The half-life of a single bolus dose of fentanyl is short because of rapid distribution throughout the body (426). However, this half-life increases with prolonged infusion once fat and muscle stores are saturated, and hepatic elimination becomes rate limiting (426). Initial single-dose bolus studies of fentanyl pharmacokinetics reported that fentanyl is relatively unaltered by liver disease (426). However, at high doses, in cirrhosis and in severe liver disease, the duration of action is markedly prolonged (426).

**Transdermal Fentanyl**

Transdermal fentanyl has not been adequately studied in hepatic failure. Hepatic failure alters skin permeability and regional blood flow to the skin, which influences drug absorption (426). Therefore, the transdermal route should also be avoided as drug absorption from that route could be unpredictable (37). **Level 5**

#### 2.6.2.7 Alfentanil

Alfentanil demonstrates complex pharmacokinetics. In liver failure associated with hypoalbuminemia, reduced protein binding leads to prolonged and pronounced analgesia per dose (426).

#### 2.6.2.8 Methadone

The influence of chronic liver disease on methadone metabolism has not been well studied (426). Methadone is 90% protein bound and its elimination half-life in normal liver function varies from 7 to 57 hours (37). With impairment of liver function there may be a three- to four-fold increase in the elimination half-life, which could to lead to further accumulation and potentially fatal adverse effects (37). Methadone is commonly used for opioid maintenance therapy in subjects with a high prevalence of liver disease. Steady state pharmacokinetics in this population do not appear to differ from that of the healthy population. However, in patients with hepatitis C, reports suggest that methadone requirements may actually be greater than anticipated. This is because hepatitis C reportedly stimulates CYP3A4, an enzyme that is responsible for the metabolism of methadone (426). As in the general population, in patients with hepatic impairment, inter-individual variability in the pharmacokinetics of methadone as well as its long half-life limit its utility.

#### 2.6.2.9 *Buprenorphine*

Buprenorphine pharmacokinetics have been inadequately studied in patients with hepatic impairment.

- Several cases of buprenorphine hepatic toxicity have been described, most frequently after intravenous use of the drug (433, 434).
- Contradictory results exist regarding the hepatotoxicity of buprenorphine in patients already presenting with liver disease, particularly hepatitis C (435, 436).
- Cicozzi et al (2012) present a case report where buprenorphine was used effectively in a terminally ill individual with significant liver disease (437).

At this time there is insufficient evidence to permit a recommendation to be made regarding the use of buprenorphine for management of cancer pain in patients with hepatic failure.

**Table 16** The Effects of Liver Disease on Opioid Pharmacokinetics
(Table reproduced from Opioids in Cancer Pain, Oxford, 2nd Ed)(426)

| Opioid | Bioavailability | Activation | Clearance |
|---|---|---|---|
| Codeine | - | + | +++ |
| Tramadol | - | + | +++ |
| Morphine sulphate | ++ | - | + |
| Oxycodone | + | - | +++ |
| Hydromorphone | ++ | - | + |
| Fentanyl | + | - | +++ |
| Alfentanil | + | - | ++ |
| Methadone | - | - | + |

Key: - no effect; + minimal effect; ++ moderate effect; +++strong effect

### 2.6.3 Non-opioid analgesics in hepatic impairment

There is very little information on paracetamol and its changes in metabolism in patients with chronic liver disease (424).

- Benson et al (2005)(438) discuss how paracetamol is often avoided in patients with chronic liver disease. The belief that paracetamol should be avoided in these patients came from the association between massive paracetamol overdose and hepatotoxicity. There is also a poor understanding of the metabolism of paracetamol in patients with liver disease. Studies of paracetamol in patients with chronic liver disease have shown that the half-life of paracetamol may be prolonged but the cytochrome P450 activity is not increased and glutathione stores are not depleted to critical levels in those taking recommended doses. Paracetamol has been studied in a variety of liver diseases without evidence of increased risk of hepatotoxicity at currently recommended doses. Therefore, paracetamol can be used safely in patients with liver disease and is a preferred weak analgesic/antipyretic because of the absence of the platelet impairment, gastrointestinal toxicity and nephrotoxicity associated with non-steroidal anti-inflammatory drugs (438). Bosilkovska and colleagues (2012) suggest that owing to the changes in the pharmacokinetics and the vulnerability of this population, it seems reasonable to limit the adult daily dose to 2g, half the suggested therapeutic dose (439).

**Level 5**

Hepatotoxicity is considered a class characteristic of NSAIDs and there is limited evidence regarding the use of NSAIDS in hepatic impairment. What evidence there is suggests that the pharmacokinetics and metabolism of ibuprofen (424) and diclofenac (423) in patients with hepatic impairment are similar those with normal liver function. Naproxen however has been shown to have reduced metabolism in hepatic impairment (424) and dose reduction is recommended (440).

**Table 17** Recommendations on the use of analgesics in liver disease (Adapted from PANG(19) and Hanna (37))

| Drug | Recommendations in liver disease | Comment |
|---|---|---|
| Codeine | Avoid use | In moderate hepatic impairment, codeine will have unpredictable efficacy and adverse effects. |
| Tramadol | Use with caution<br>Avoid in severe | In moderate hepatic impairment, tramadol will have unpredictable efficacy and adverse effects. If use cannot be avoided, increase the dosage interval. |
| Morphine sulphate | Use with caution | Moderate impairment – use lower doses and extend dosing interval. In severe, hepatic impairment, oral bioavailability may equal that of intravenous. |
| Oxycodone | Use with caution<br>Avoid in severe | Moderate impairment – use lower doses with a minimum dosing interval of 6 hourly for normal release products. |
| Targin® (Oxycodone/ naloxone) | Use with caution<br>Avoid in moderate to severe liver disease | Naloxone component may be systemically absorbed and precipitate pain and opioid withdrawal. |
| Hydromorphone | Use with caution | Dosage reduction necessary. In severe hepatic impairment oral bioavailability may increase significantly. Monitor patient carefully for adverse effects. |
| Fentanyl | Use with caution | Avoid transdermal products. Single doses appear unaltered by liver disease. May be suitable for the treatment of breakthrough pain. |
| Alfentanil | Use with caution | Dosage reduction necessary. |
| Methadone | Not advised | Not advised in moderate liver failure due to the risk of accumulation and fatal adverse effects. |

**Recommendation 39 Opioids in hepatic impairment**
**The following are responsible for implementation of recommendation 39:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>There is very limited evidence available to evaluate the use of opioids in patients with liver impairment. Liver disease can alter the pharmacokinetics of opioids. | |
| **Key recommendation** | |
| C | In advanced liver impairment:<br><br>Opioids should be used with caution in patients with advanced liver disease. Dosage recommendation should be patient specific and specialist advice sought.<br><br>The transdermal route should be avoided, as drug absorption can be variable and unpredictable.<br><br>Sustained release preparations should be avoided. |

## 2.7 Non-pharmacological approaches to the management of cancer pain

**Introduction**
Along with opioid and non-opioid pharmacological interventions, it is important to consider non-pharmacological interventions which have the potential to control cancer pain and improve quality of life[2]. Interventions such as chemotherapy, hormone therapy and novel biologic agents have the potential to modify disease progression and to improve pain as a result, dependent on individual patient and tumour characteristics. Surgery and radiotherapy also may have an analgesic, or direct disease-modifying effect. In this section, the roles of radiotherapy, percutaneous vertebroplasty and anaesthetic procedures are discussed[2].

### *2.7.1 Radiotherapy for pain secondary to bone metastases*

Radiotherapy may be delivered in single or multiple doses (or 'fractions'). Where pain is limited to a single or limited number of sites, radiotherapy may be delivered via external beam radiotherapy. Where symptomatic lesions are widespread, radiotherapy may be delivered via hemibody radiotherapy or, more commonly nowadays, in the form of radioisotope agents.

2 The primary focus of this guideline is to make recommendations based on best and most up to date evidence on the pharmacological management of cancer pain in adults. However, as non-phamacological approaches are commonly used in tandem with pharmacological ones, a short section on the non-pharmacological management of cancer pain has been included to provide an overview of this area and detail consensus-based guidance.

The efficacy of radiotherapy for pain related to bone metastases has been demonstrated in several high quality RCTs and systematic reviews.

- A Cochrane systematic review performed by McQuay et al (2000) demonstrated the achievement of complete pain relief at one month in 27% of patients, and at least 50% pain relief in 41% of patients at some point in the duration of follow up of the trials (441). The pattern of pain relief after external beam radiotherapy for localised bone pain was shown to evolve over four to six weeks from treatment, with 50% of patients responding within two weeks of treatment (441). Fifty-two percent of patients who had complete pain relief achieved it within four weeks, and the median duration of complete relief was 12 weeks (441). **Level 1b**

#### *2.7.1.1 Single versus multiple fractionation*

Two systematic reviews demonstrated no difference in pain relief obtained with single fraction (SF), compared to multiple fraction (MF) radiotherapy:

- Chow et al (2007) performed a systematic review of 16 RCTs involving over 5000 patients (442). This demonstrated a 23% complete response rate for SF versus 24% for MF radiotherapy. However, a significantly higher re-treatment rate was demonstrated in the SF group. No significant different in toxicity rates following SF and MF radiotherapy was demonstrated.
- Sze et al (2004) performed a systematic review of 11 RCTs, comprising 3621 patients (443). This demonstrated a response rate of 60% for SF versus 59% for MF radiotherapy. Complete response rates were 34% for SF, and 32% for MF radiotherapy. However, 21.5% of the SF group required re-treatment versus 7.4% of the MF group. There was also a higher rate of pathological fractures post SF treatment (3% versus 1.6%)(2, 443). **Level 1b**

Even where prognosis is short, referral for radiotherapy may be warranted in order to control refractory symptoms. When deciding upon a fractionation schedule, SF radiotherapy is a valid option for patients with advanced cancer, particularly when the time to pathological fracture or need for re-treatment would be expected to exceed the predicted prognosis of the patient.

#### *2.7.1.2 Radioisotopes*

Radioisotope treatment involves the administration of radioisotopes, which are attracted physiologically to sites of bone mineralisation. This delivers localised radiotherapy to multiple sites of bone metastasis, and is effective for the management of scattered metastatic bone pain, for example multiple metastases associated with prostate cancer.

- A Cochrane systematic review, regarding the efficacy of radioisotopes for metastatic bone pain, was performed by Roque et al (2003). Four trials, involving 325 patients, demonstrated weak evidence of a small beneficial effect of radioisotopes for pain over one to six months. There was a higher incidence of secondary effects such as pancytopenia demonstrated post radioisotope treatment, compared to local field external beam radiotherapy (444). **Level 1b**

Available radioisotopes include strontium and rhenium.

- Finlay et al (2005) performed a systematic review and demonstrated no significant difference between strontium and other radioisotopes in terms of pain response rates or toxicity (2, 445). **Level 1b**

#### *2.7.1.3 Radiotherapy for pain in sites other than bone*

External beam radiotherapy is an effective management option to reduce pain and other symptoms secondary to disease at sites other than bone, for example where there is local tumour infiltration of the chest wall, head and neck, or pelvis (446). Although there is a lack of randomised trial data regarding radiotherapy for such indications, its use is widespread, and is recommended in many consensus clinical guidelines.

**Recommendation 40 Radiotherapy**
**The following are responsible for implementation of recommendation 40:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **Key finding**<br>Radiotherapy is an effective and well-tolerated treatment for the management of pain related to bone metastases. | |
| **Key recommendation** | |
| **A** | Patients with pain secondary to bone metastases that is difficult to control by pharmacological means alone should be referred to a radiation oncologist for consideration of radiotherapy. |

### *2.7.2 Percutaneous cementoplasty*

Osteolytic involvement of the spine by cancer may cause loss of vertebral height, which can be associated with significant morbidity and mortality (2). Percutaneous cementoplasty involves the injection of acrylic bone cement into malignant bone cavities in order to relieve pain, and/or to stablise the bone. Vertebroplasty involves the injection of bone cement into the vertebral body in order to stabilise the fractured vertebra, restore vertebral height and relieve pain (2).

Compared to radiotherapy, vertebroplasty may provide more immediate relief than for painful vertebral metastases. Vertebroplasty may be better tolerated than surgery if performance status is poor (2). **Level 5**

Balloon kyphoplasty uses an inflatable bone tamp to restore the vertebral body towards its original height, while creating a cavity to be filled with bone cement (2, 446). Kyphoplasty is more time-consuming and more often requires a general anaesthetic, but is associated with fewer complications than vertebroplasty (446). **Level 3**

#### 2.7.2.1 Vertebroplasty

Case series involving patients with both osteoporosis and metastatic cancer demonstrate consistent benefit in terms of sustained pain relief, which may last up to two years (448-450). Complications include allergic reaction, infection, haemorrhage or fracture of vertebra, rib or sternum (451). Cement leakage may occur, although rarely causes clinical complications (452).

**Level 4**

#### 2.7.2.2 Bone metastases in sites other than the spine

Pain control and improved mobility may be achieved with percutaneous injection of acrylic cement into acetabular or pelvic bones which have been affected by lytic bone metastases (453-455).

**Level 4**

**Recommendation 41 Percutaneous cementoplasty**
**The following are responsible for implementation of recommendation 41:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| **Best practice point** |
|---|
| The selection and management of patients requiring percutaneous cementoplasty should be carried out in the context of a multidisciplinary team, which may include specialists in radiology, oncology, radiotherapy, orthopaedics, pain management and palliative care. |

| **Key finding** | |
|---|---|
| Percutaneous cementoplasty is an effective and well-tolerated intervention for pain secondary to destructive bone metastases within the spine or pelvis. | |
| **Key recommendation** | |
| C | **41.1** Patients with difficult to control pain secondary to malignant vertebral collapse should be referred for consideration of vertebroplasty, or kyphoplasty. |
| C | **41.2** Patients with difficult to control pain secondary to destructive pelvic metastases should be referred for consideration of percutaneous cementoplasty, where this technique is available. |

### 2.7.3 Anaesthetic procedures

Several anaesthetic procedures are available for the management of pain, including pain caused by cancer. There is however a limited amount of high quality evidence for the use of anaesthetic procedures in the management of cancer pain. Consensus-based guidelines suggest that such techniques may be considered where conventional oral or parenteral therapies are unsuccessful, or side-effects are intolerable (2, 19).

**Level 5**

#### 2.7.3.1 Nerve block

Neurolytic procedures utilise substances such as ethanol and phenol to destroy neural tissue. Options include the use of a coeliac plexus block for pain originating in the pancreas / upper abdomen, superior hypogastric plexus block for lower abdominal pain, intercostal or peripheral nerve blocks (52).

- Four RCTs and two cohort studies compare neurolytic coeliac plexus block to either placebo (456-458) or another intervention, such as splanchnic nerve block (459, 460). The largest RCT in this group, performed by Wong et al (2004) demonstrated an analgesic benefit with coeliac plexus block, although no reduction in opioid consumption, quality of life or survival were demonstrated (458). **Level 1b**
- A meta-analysis of RCTs by Eisenberg et al (1995) demonstrated the effectiveness of a neurolytic coeliac plexus block for pancreatic pain, with superior results over analgesics, for a duration of more than three months, in 70 – 90% of patients. Adverse effects included diarrhoea and hypotension, but were transient and mild in most patients (461). **Level 1a**

There is limited evidence available for the use of nerve blocks other than coeliac plexus blocks in the cancer setting.

#### *2.7.3.2 Neuraxial opioids (See also section 2.3.2.3 Spinal Opioids)*

Opioids can be delivered by the spinal or epidural routes, and may provide analgesia at a lower dose than that required for systemic administration. This may be useful where pain is refractory to systemic opioids, or where intolerable side-effects are experienced with systemic opioids (221).

There are few high quality trials of neuraxial opioids, although these techniques are in widespread use for the management of both chronic and cancer pain (2). Due in part to improvements in cancer pain management in recent years, including better pharmacological options and more widespread use of palliative radiotherapy, the number of patients requiring neuraxial treatment are small, limiting opportunities to perform RCTs (221).

- Smith et al (2002) performed a large multi-centre randomised study of intrathecal opioid use and demonstrated a benefit in terms of analgesia obtained for refractory cancer pain and survival, compared to standard medical management was demonstrated (462). **Level 1b**
- A review of the evidence for epidural, subarachnoid, and intracerebroventricular (ICV) routes of opioid administration found limited evidence, but similar efficacy for all neuraxial routes (463). **Level 2a**
- A systematic review of the efficacy of spinal opioids in adult cancer pain was performed by Kurita et al (2011)(221). Nine RCTs, two non-randomised cohort studies, 28 uncontrolled prospective studies, and five case series were identified. The overall quality of the evidence was found to be low, with even the RCTs having severe methodological limitations.
  - Agents used via the spinal route include morphine sulphate as first line, and bupuvicaine and clonidine as second line agents in combination with morphine sulphate. No evidence was found to support the use of one agent over another.
  - On the basis of this review, the authors recommend neuraxial opioid therapy only if systemic therapy has failed due to either inadequate analgesia, or intolerable side-effects; and only when oral, transdermal, subcutaneous and parenteral opioids have been exhausted.
- A systematic review of the use of spinal analgesia in 2012 (464) found little new evidence in the last decade to support its use in cancer related pain. However, the authors recommended that spinal analgesia should be considered in cases where cancer pain is refractory to optimization of opioid therapy, side effects of systemic opioids are intolerable, or where opioid induced hyperalgesia exists. **Level 1b**

**Recommendation 42 Neuraxial opioids**
**The following are responsible for implementation of recommendation 42:**
*CEO/General Managers/Line managers are responsible for ensuring healthcare staff are aware of this guideline. All healthcare staff caring for patients with cancer are responsible for implementation.*

| | |
|---|---|
| **B** | Neuraxial opioid therapy for management of cancer pain should be considered where pain is refractory to or intolerable side-effects are experienced with systematic opioids; and should be used only when oral, transdermal, subcutaneous and parenteral options have been exhausted. |

# 3 Appendices and References

## Appendix I: Guideline Development Group and conflict of interest

The following lists the active members who contributed to the drafting and amending the guideline.

- **Dr Michael Lucey** (Chair), Consultant in Palliative Medicine, Milford Care Centre & UL Hospitals, Limerick
  Conflicts of Interest: nothing to declare

- **Dr Lucy Balding**, Consultant in Palliative Medicine, Our Lady's Hospice & Care Services, Harold's Cross, Dublin and St James's Hospital, Dublin
  Conflicts of Interest: nothing to declare

- **Dr Sarah McLean**, Specialist Registrar in Palliative Medicine, Royal College of Physicians of Ireland
  Conflicts of Interest: nothing to declare

- **Ms Fiona McGrehan**, Clinical Pharmacist, Our Lady's Hospice & Care Services, Harold's Cross, Dublin
  Conflicts of Interest: nothing to declare

- **Ms Cliona Hayden**, Clinical Pharmacist, Our Lady's Hospice & Care Services, Harold's Cross, Dublin
  Conflicts of Interest: nothing to declare

- **Dr Karen Ryan**, Consultant in Palliative Medicine, Clinical Lead, National Clinical Programme for Palliative Care
  Conflicts of Interest: nothing to declare

**Additional Contributions and Review**

The GDG was supported by:

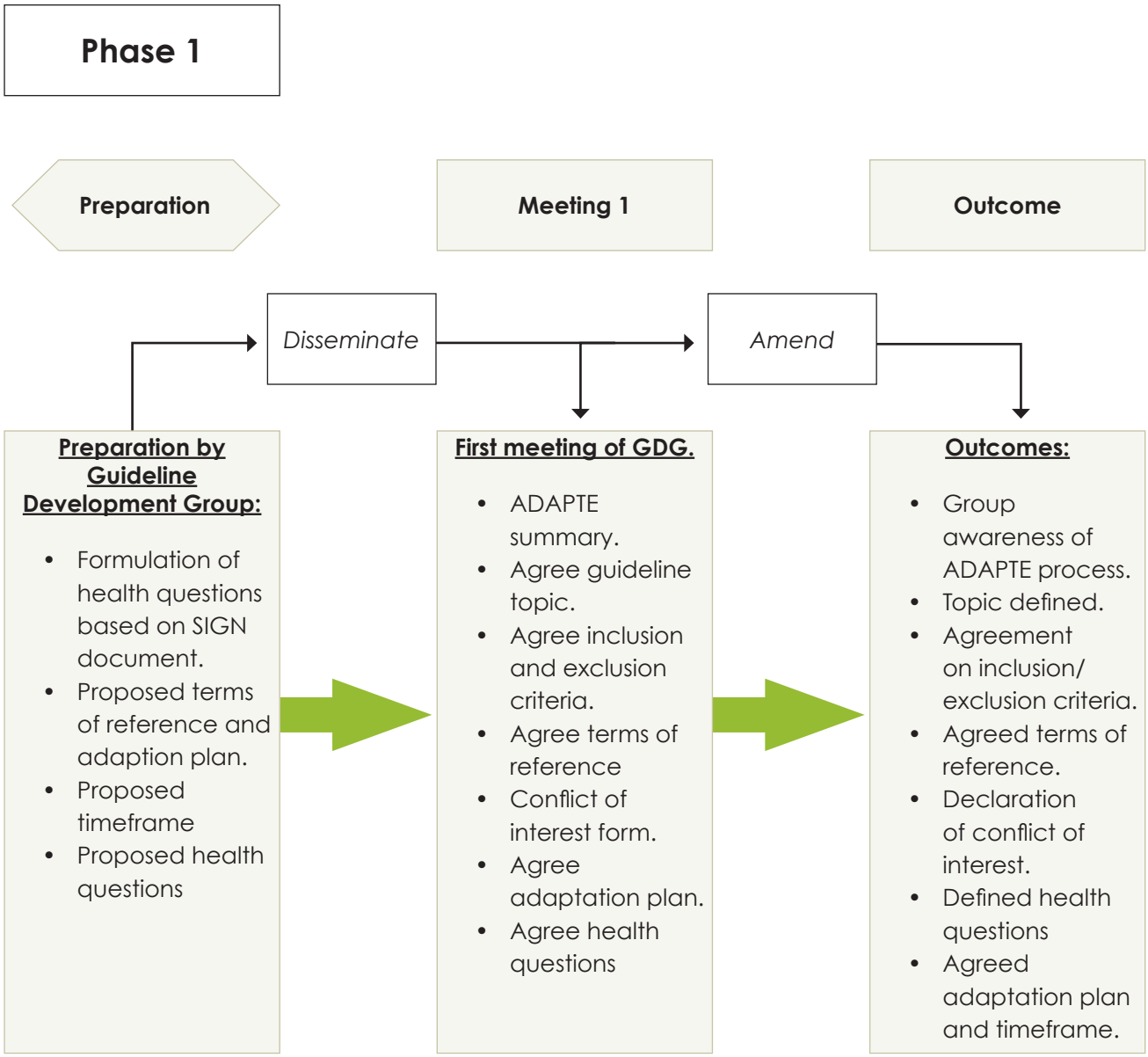
- Mr Gethin White, Librarian, Health Service Executive, Ms Joanne Callinan, Librarian, Milford Hospice, Limerick; Ms Aine MhicAodhagain, Librarian, St Francis Hospice, Raheny; Ms Fiona Lawlor, Librarian, Our Lady's Hospice and Care Services, Harolds Cross; Ms Aoife Lawton, Librarian, Health Service Executive; Mr Padraig Manning, Librarian, Health Service Executive.
- Dr Des McMahon, Specialist Registrar in Palliative Medicine, Royal College of Physicians of Ireland who in collaboration with the GDG, developed the executive summary and quick reference guides.
- Mr Brian Lee, Programme Manager, National Clinical Programme for Palliative Care, replaced by Ms Sinéad Fitzpatrick in December 2013 co-ordinated meetings, managed the consultation process and formatting the document.
- Mr Louis Lavelle, Programme Co-ordinator, Quality and Clinical Care, RCPI developed the baseline assessment tool, audit tool and action plan template.
- Ms Anita Nicholson, Administrator, Royal College of Physicians in Ireland (RCPI) assisted in formatting early drafts of the document.

**Additional Members ('Guideline Steering Group'):**

Additional members of the guideline development group known as the Guideline Steering Group reviewed the draft material and provided commentary at key stages of the process as outlined in Appendix II.

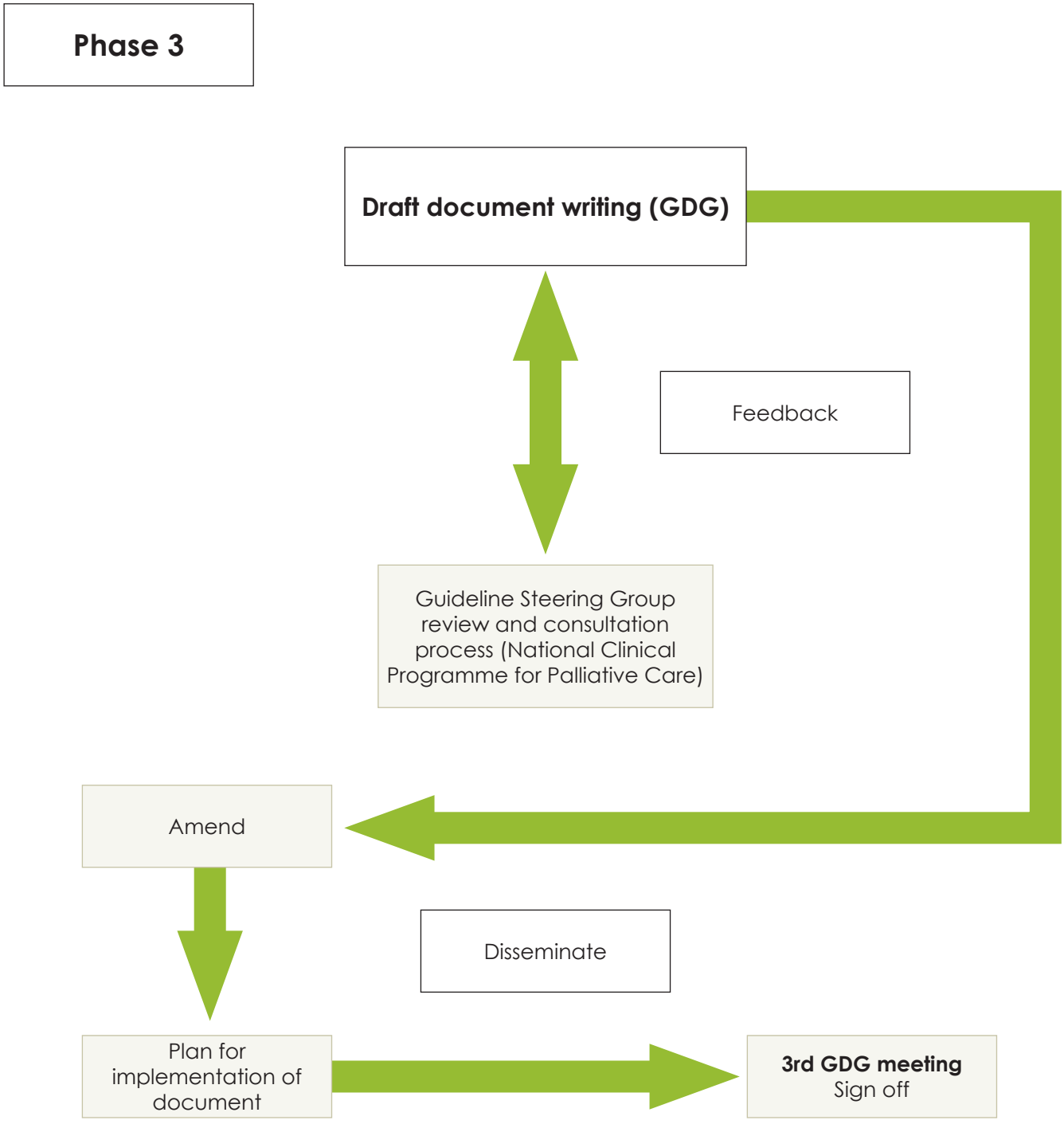
| |
|---|
| Dr Brian Creedon, Regional Lead for HSE South, National Clinical Programme for Palliative Care |
| Dr Stephen Higgins, Regional Lead for HSE DML, National Clinical Programme for Palliative Care |
| Dr Aisling O'Gorman, Regional Lead for HSE DNE, National Clinical Programme for Palliative Care |
| Dr Feargal Twomey, Regional Lead for HSE West, National Clinical Programme for Palliative Care |
| Dr Mary Devins, Paediatric Lead, National Clinical Programme for Palliative Care |
| Ms Lorna Peelo-Kilroe, Nursing Lead, National Clinical Programme for Palliative Care |
| Ms Mary Marsden, Nursing representative, National Clinical Programme for Palliative Care |
| Ms Ger Treacy, Nursing representative, National Clinical Programme for Palliative Care |
| Ms Valerie Keane, Social Work representative, National Clinical Programme for Palliative Care |
| Ms Shirley Reale / Ms Deirdre Row, Therapy professions representatives, National Clinical Programme for Palliative Care |
| Ms Grainne Tipping / Ms Ann O'Connor, Pharmacy representative, National Clinical Programme for Palliative Care |
| Ms Sheilagh Reaper Reynolds, HSE Representative |
| Ms Eileen O'Leary, HSE representative |
| Ms Mo Flynn, Representative for the Voluntary Hospices Group |

# Appendix II: Guideline Development: adaptation plan (based on the ADAPTE Collaboration process)



**Phase 2**


Guideline and literature search* (core group) (*2011, updated search conducted 2014)
• Screen Guidelines/ Literature (AGREE II)
• Reduce Guidelines/ Literature (AGREE II) (core group)
Main Guideline assessment (AGREE II) (core group)
Write up assessment documentation/ matrices/ graphs/ recommendations (core group)
Write up assessment documentation/ matrices/ graphs/ recommendations (core group)
Disseminate to guideline group
**2nd guideline group meeting.** Review assessments Agree recommendations


Phase 3
Draft document writing (GDG)
Feedback
Guideline Steering Group review and consultation process (National Clinical Programme for Palliative Care)
Amend
Disseminate
Plan for implementation of document
3rd GDG meeting
Sign off

# Appendix III: Agree II scores

**Table 18** Agree II scores

| | |
|---|---|
| **SIGN 106 (2)** | |
| DOMAIN 1 (Scope & Purpose): 100%<br>DOMAIN 2 (Stakeholder Involvement): 96.3%<br>DOMAIN 3 (Rigour of Development): 89.5% | DOMAIN 4 (Clarity of Presentation): 92.6%<br>DOMAIN 5 (Applicability): 83.3%<br>DOMAIN 6 (Editorial Independence): 100% |
| **ESMO (41)** | |
| DOMAIN 1 (Scope & Purpose): 7.4%<br>DOMAIN 2 (Stakeholder Involvement): 3.7%<br>DOMAIN 3 (Rigour of Development): 7.6% | DOMAIN 4 (Clarity of Presentation): 9.2%<br>DOMAIN 5 (Applicability): 0%<br>DOMAIN 6 (Editorial Independence): 22.2% |
| **GAIN (73)** | |
| DOMAIN 1 (Scope & Purpose): 77.7%<br>DOMAIN 2 (Stakeholder Involvement): 61.1%<br>DOMAIN 3 (Rigour of Development): 22.9% | DOMAIN 4 (Clarity of Presentation): 85.2%<br>DOMAIN 5 (Applicability): 37.5%<br>DOMAIN 6 (Editorial Independence): 19.4% |
| **NCCN (18)** | |
| DOMAIN 1 (Scope & Purpose): 63.9%<br>DOMAIN 2 (Stakeholder Involvement): 41.7%<br>DOMAIN 3 (Rigour of Development): 41.7% | DOMAIN 4 (Clarity of Presentation): 97.2%<br>DOMAIN 5 (Applicability): 39.6%<br>DOMAIN 6 (Editorial Independence): 66.7% |
| **Oncology Nursing Society (20)** | |
| DOMAIN 1 (Scope & Purpose): 63.9%<br>DOMAIN 2 (Stakeholder Involvement): 41.7%<br>DOMAIN 3 (Rigour of Development): 64.9% | DOMAIN 4 (Clarity of Presentation): 50%<br>DOMAIN 5 (Applicability): 22.9%<br>DOMAIN 6 (Editorial Independence): 100% |
| **PANG (19)** | |
| DOMAIN 1 (Scope & Purpose): 25.9%<br>DOMAIN 2 (Stakeholder Involvement): 31.5%<br>DOMAIN 3 (Rigour of Development): 34% | DOMAIN 4 (Clarity of Presentation): 85.2%<br>DOMAIN 5 (Applicability): 27.8%<br>DOMAIN 6 (Editorial Independence): 25% |

# Appendix IV: Recommendation matrix

**Table 19** Recommendation matrix

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| **Title of guideline** | **Control of pain in adults with cancer** | **General palliative care guidelines for the management of pain at the end of life in adult patients** | **Adult Cancer Pain: Clinical Practice Guidelines in Oncology** | **Putting Evidence Into Practice: What Are the Pharmacologic Interventions for Nociceptive and Neuropathic Cancer Pain in Adults?** | **Palliative Adult Network Guidelines** |
| Publication year | 2008 | 2011 | 2010 | 2009 | 2011 |
| Overall score (out of 7) | 6 | 5.3 | 6 | 3 | 5.3 |
| Rigour | 89.5 | 22.9 | 41.7 | 64.9 | 34 |
| Overall quality assessment<br>• Stongly recommend<br>• Recommend with alterations<br>• Would not recommend<br>• Unsure | Stongly recommend | Recommend with alterations | Recommend with alterations | Recommend with alterations | Recommend with alterations |
| Algorithms / tools provided? | Yes | Yes | Guideline provided in format of multiple algorithms | Yes | No |
| Description | • Quick reference guide<br>• App<br>• Patient and carers booket<br>• NHS education training module | • Training powerpoint<br>• Patient information leaflet<br>• Audit assessment tool | | • Clinical practice guidelines table<br>• Pain assessment and management evidence table<br>• Patient-focused instruction sheets | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health questions | | | | | |
| Health question 1: | Is there any new evidence on pain assessment? | | | | |
| Is question addressed? | Yes | Yes | Yes | No | Yes |
| Specific recommendation | The patient should be the prime assessor of his or her pain.<br><br>Comprehensive chronic pain assessment should include routine screening for psychological distress.<br><br>Patient beliefs concerning pain should be assessed and discussed as part of a comprehensive, biopsychosocial cancer pain assessment. | In keeping with the "Total Pain" model, assessment should consider the following domains: physical, psychosocial, spiritual.<br><br>The patient, if competent and able to communicate, is the most reliable assessor of pain, and where possible should be the prime judge of their pain | A comprehensive evaluation is essential to ensure proper pain management.<br><br>Patient's self-report of pain is the standard of care. If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized. | - | Accurate assessment of pain is essential to plan appropriate interventions or treatments |
| Level of evidence | 3 | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Graves KD. Social cognitive theory and cancer patients' quality of life: a meta analysis of psychosocial intervention components. Health Psychol 2003;22(2):210-9.<br>Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. Cancer 1994; 74(9):2570-8.<br>Passik S, Dugan W, McDonald M, et al. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 1998; 16(4): 1594 600.<br>Lai Y, et al. Relationship between pain-specific beliefs and adherence to analgesic regimens in Taiwanese cancer patients: a preliminary study. J Pain Symptom Manage 2002;24(4):415-23. | Saunders C.M. (1988) Spiritual pain. Journal of Palliative Care, 4(3) Sept 29-32<br><br>Scottish Intercollegiate Guidelines Network (SIGN ) (2008) Control of pain in adults with cancer:<br>A national clinical guideline, 7-9, Edinburgh: Scottish Intercollegiate Guidelines Network. www.<br>sign.ac.uk/pdf/ SIGN106.pdf | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | Zech D, Grond S, Lynch J, Hertel D, Lehmann K. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. Pain 1995;63(1):65-76. Grossman S, Sheidler V, Swedeen K, Mucenski J, Piantadosi S. Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage 1991;6(2):53-7. | | | | |
| Health question 2: | Is there any evidence that the use of pain assessment tools improves patient's pain scores? | | | | |
| Is question addressed? | Yes | Yes | Yes | No | No |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Specific recommendation | Patients with cancer pain should have treatment outcomes monitored regularly using visual analogue scales, numerical rating scales or verbal rating scales.<br><br>Self assessment pain scales should be used in patients with cognitive impairment, where feasible.<br><br>Observational pain rating scales should be used in patients who cannot complete a self-assessment scale. | Many different pain assessment tools are available, with no universally accepted tool | Pain intensity rating scales can be used as part of universal and comprehensive pain assessment. At minimum, patients should be asked about 'current' pain as well as 'worst' pain and 'usual' pain in the past 24 houls.<br>For comprehensive assessment also include 'worst pain in the last week', 'pain at rest' and 'pain with movement'.<br>Pain Assessment in the Nonverbal Patient: In the absence of self-report, observation of behavior is a valid approach to pain assessment with the understanding that behaviors may also indicate another source of distress, such as emotional distress. Potential causes and the context of the behavior must | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | | | be considered when making pain treatment decisions. A multifaceted approach is recommended that combines direct observation, family/ caregiver input, and evaluation of response to pain medicines or nonpharmacologic interventions | | |
| Level of evidence | 3-4 | - | - | - | - |
| Source of recommendation (reference/ evidence) | Boisvert M, Cohen S. Opioid use in advanced malignant disease: why do different centers use vastly different doses? A plea for standardized reporting. J Pain Symptom Manage 1995;10(8):632-8.<br><br>de Wit R, van Dam F, Abu-Saad HH, Loonstra S, Zandbelt L, van Buuren A, et al. Empirical comparison of commonly used measures to evaluate pain treatment in cancer patients with chronic pain. J Clin Oncol 1999;17(4):1280-7. | Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale, Acta Psychiatrica Scandinavica, 67,6,361-370.<br><br>Anandarajah, G. and Hight, E. (2001) 'Spirituality and Medical Practice: Using the HOPE Questions as a Practical Tool for Spiritual Assessment'. American Family Physician 63: 81-8,89. | Ware LJ, Epps CD, Herr K, Packard A. Evaluation of the Revised Faces Pain Scale, Verbal Descriptor Scale, Numeric Rating Scale, and Iowa Pain Thermometer in older minority adults. Pain Manag Nurs 2006;7:117-125.<br><br>Herr K, Coyne P, Key T, et al. Pain assessment in the nonverbal patient: position statement with clinical practice recommendations. Pain Manag Nurs 2006;7:44-52. | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | Caraceni A, Cherny N, Fainsinger R, Kaasa S, Poulain P, Radbruch L, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an expert working group of the European Association of Palliative Care. J Pain Symptom Manage 2002;23(3):239-55.<br><br>Wallenstein S, Heidrich Gr, Kaiko R, Houde R. Clinical evaluation of mild analgesics: the measurement of clinical pain. Br J Clin Pharmacol 1980;10(Suppl 2):319-27S.<br><br>Littman G, Walker B, Schneider B. Reassessment of verbal and visual analog ratings in analgesic studies. Clin Pharmacol Therap 1985;38(1):16-23. | | | | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | Mystakidou K, Parpa E, Tsilika E, Kalaidopoulou O, Georgaki S, Galanos A, et al. Greek McGill pain questionnaire: Validation and utility in cancer patients. J Pain Symptom Manage 2002;24(4):379-87.<br><br>Caraceni A, Mendoza T, Mencaglia E, Baratella C, Edwards K, Forjaz M, et al. A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). Pain 1996;65(1):87-92. | | | | |
| Health question 3: | Is there any evidence to support the association of cancer pain with psychological distress? | | | | |
| Is question addressed? | Yes | Yes | Yes | No | No |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | Comprehensive chronic pain assessment should include routine screening for psychological distress.<br><br>Screening for psychological distress should be carried out using a validated tool. | Pain is more than just a physical phenomenon and requires the psychological, social and spiritual dimensions to be addressed on an individual basis | Comprehensive chronic pain assessment should include screening for psychological distress. | - | - |
| Level of evidence | 1++ | - | - | - | - |
| Source of recommendation (reference/ evidence) | Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. Cancer 1994;74(9):2570-8.<br><br>Passik S, Dugan W, McDonald M, Rosenfeld B, Theobald D, Edgerton S. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 1998;16(4):1594-600. | Saunders, C (1967) The Management of Terminal Illness. London. Edward Arnold<br><br>Clark.D (1999) 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958-1967.Social Science Medicine. Sep;49(6):727-36. | - | | - |
| Health question 4: | What is the evidence to support the use of tramadol in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | No | Yes |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | There is insufficient evidence available to make a recommendation on the use of tramadol. | For mild to moderate pain<br>A weak opioid +/- non-opioid +/- an adjuvant should be prescribed regularly. Avoid rotation to other weak opioids. | Guidance on prescribing tramadol provided within algorithms | - | For mild to moderate pain a non-opioid plus a weak opioid +/- an adjuvant should be prescribed regularly. Avoid rotation to other weak opioids. |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | SIGN 106 baseline document | - | - | - |
| Health question 5: | What is the evidence to support the use of codeine in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | 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. | For mild to moderate pain<br>A weak opioid +/- non-opioid +/- an adjuvant should be prescribed regularly. Avoid rotation to other weak opioids. | Guidance on prescribing codeine provided within algorithms | Opioids, including codeine, are recommended for moderate to severe cancer-related pain | For mild to moderate pain a non-opioid plus a weak opioid +/- an adjuvant should be prescribed regularly. Avoid rotation to other weak opioids. |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | SIGN 106 baseline document | - | Tassinari et al., 2008; Wiffen & McQuay, 2007; Wootten, 2004). | - |
| Health question 6: | What is the evidence to support the use of tapentadol in a cancer pain setting? | | | | |
| Is question addressed? | No | No | No | No | No |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | - | - | - | - | - |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | - |
| Health question 7: | What is the evidence to support the use of morphine in a cancer setting? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |
| Specific recommendation | Oral morphine is recommended as first line therapy to treat severe pain in patients with cancer. | Morphine is the opioid with most evidence supporting its use and is therefore considered the first line oral strong opioid when renal and hepatic function are normal | In patients not previously exposed to opioids, morphine is generally considered the standard preferred starting drug | Opioids, including morphine, are recommended for moderate to severe cancer-related pain | Morphine remains the gold standard oral opioid.<br><br>A trial of alternative opioids may be considered for moderate to severe pain where dose titration is limited by side effects of current opioid. |
| Level of evidence | 3-4 | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Zech D, Grond S, Lynch J, Hertel D, Lehmann K. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. Pain 1995;63(1):65-76.<br><br>Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer 1987;59(4):850-6.<br><br>Hanks G, Conno F, Cherny N, Hanna M, Kalso E, McQuay H, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Canc 2001;84(5):587-93. | Wiffen PJ, McQuay HJ (2010) Oral morphine for cancer pain (review) The Cochrane library<br>2010 issue 8 | Klepstad P, Kaasa S, Borchgrevink PC. Start of oral morphine to cancer patients: effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine. Eur J Clin Pharmacol 2000;55:713–719.<br><br>Klepstad P, Kaasa S, Skauge M, Borchgrevink PC. Pain intensity and side effects during titration of morphine to cancer patients using a fixed schedule dose escalation. Acta Anaesthesiol Scand 2000;44:656–664. | Wiffen, P.J., McQuay, H.J. (2007). Oral morphine for cancer pain. Cochrane Database of Systematic Reviews, 4, CD003868.<br><br>Maltoni, M., Scarpi, E., Modonesi, C., Passardi, A., Calpona, S., Turriziani,<br>A., et al. (2005). A validation study of the WHO analgesic ladder: A two-step vs. three-step strategy. Supportive Care in Cancer, 13(11), 888–894. | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | 157. Ross J, Riley J,<br><br>Quigley C, Kl. W. Clinical pharmacology and pharmacotherapy of opioid switching in cancer patients Oncologist 2006;11(7):765-73 | | | | |
| Health question 8: | What is the evidence to support the use of oxycodone in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | No recommendation formulated | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | Guidance on prescribing oxycodone provided within algorithms | Opioids, including oxycodone, are recommended for moderate to severe cancer-related pain<br><br>Wootten, M. (2004). Morphine is not the only analgesic in palliative care: Literature review. Journal of Advanced Nursing, 45(5), 527–532. | The decision to use a specific opioid preparation should be based on a combination of factors:<br>• pain characteristics (onset, duration),<br>• the product characteristics (pharmacokinetics, pharmacodynamics)<br>• the patient's previous response to opioids (efficacy, tolerability)<br>• the patient's preference for an individual preparation. |
| Level of evidence | - | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | - | SIGN 106 baseline document | - | Reid, C.M., Martin, R.M., Sterne, J.A., Davies, A.N., & Hanks, G.W. (2006). Oxycodone for cancer-related pain: Meta-analysis of randomized controlled trials. Archives of Internal Medicine, 166(8), 837–843. | - |
| Health question 9: | What is the evidence to support the use of hydromorphone cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | No recommendation formulated | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | Guidance on prescribing hydromorphone provided within algorithms | Opioids, including hydromorphone, are recommended for moderate to severe cancer-related pain | The decision to use a specific opioid preparation should be based on a combination of factors:<br>• pain characteristics (onset, duration),<br>• the product characteristics (pharmacokinetics, pharmcodynamics)<br>• the patient's previous response to opioids (efficacy, tolerability)<br>• the patient's preference for an individual preparation. |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | http://emc.medicines.org.uk/medicine/1228/SPC/Palladone+SR+capsules/, date accessed 03.02.2011 | - | Wootten, M. (2004). Morphine is not the only analgesic in palliative care: Literature review. Journal of Advanced Nursing, 45(5), 527–532. | - |
| Health question 10: | What is the evidence to support the use of fentanyl in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |
| Specific recommendation | In patients with stable pain who are unable to swallow oral medication transdermal administration of opioids should be considered. | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids. | It is useful for patients who have difficulty swallowing or who cannot take oral medications | Transdermal opioid patches should only be used for stable pain and preferably only if there are particular difficulties or compliance issues with oral medication<br><br>Transdermal preparations should not be commenced in patients with uncontrolled pain or who are moribund. |
| Level of evidence | - | - | - | - | - |

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|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | - | SIGN 106 baseline document | Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001;84:587–593. | Pergolizzi, S., Iati, G., Santacaterina, A., Palazzolo, C., Di Pietro, A., Garufi, G., et al. (2006). Treatment planning in patients with bone metastases. Final results of a prospective study using premedication with fentanyl to improve irradiation reproducibility. Supportive and Palliative Cancer Care, 2(2), 71–75.<br><br>Wootten, M. (2004). Morphine is not the only analgesic in palliative care: Literature review. Journal of Advanced Nursing, 45(5), 527–532. | - |
| Health question 11: | What is the evidence to support the use of alfentanil in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | No | No | Yes |

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| Specific recommendation | See renal failure | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | - | - | The decision to use a specific opioid preparation should be based on a combination of factors:<br>• pain characteristics (onset, duration),<br>• the product characteristics (pharmacokinetics, pharmacodynamics)<br>• the patient's previous response to opioids (efficacy, tolerability)<br>• the patient's preference for an individual preparation. |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | http://emc.medicines.org.uk/medicine/930/SPC/Rapifen/ , accessed 03.02.2011<br><br>http://emc.medicines.org.uk/medicine/931/SPC/Rapifen+Intensive+Care/ accessed 03.02.2011 | - | - | - |
| Health question 12: | What is the evidence to support the use of buprenorphine in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | No | No | Yes |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | No recommendation formulated | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | - | - | The decision to use a specific opioid preparation should be based on a combination of factors:<br>• pain characteristics (onset, duration),<br>• the product characteristics (pharmacokinetics, pharmacodynamics)<br>• the patient's previous response to opioids (efficacy, tolerability)<br>• the patient's preference for an individual preparation. |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | http://emc.medicines.org.uk/medicine/8864/SPC/Transtec+35%2c + 52.5+and+70+ micrograms++ transdermal+patch/, date accessed 03.02.2011<br><br>http://emc.medicines.org.uk/ medicine/16787/ SPCBuTrans+5%2c+10+ and+20ug+h+ Transdermal+Patch/, date accessed 03.02.2011 | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Health question 13: | What is the evidence to support the use of methadone in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |
| Specific recommendation | No recommendation formulated | Initiation and titration of methadone for pain control should only be carried out under specialist supervision due to complex titration regimens and risks of toxicity. | Practitioners are advised to consult with a pain or palliative care specialist if they are unfamiliar with methadone prescribing. | Methadone should only be prescribed by experienced clinicians with skill in methadone conversions and dosing. | Initiation and titration of methadone should only be carried out under specialist supervision due to complex titration regimens and risks of toxicity |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | http://emc.medicines.org.uk/medicine/10721/SPC/ Methadone+Hydrochloride+DTF+1mg+1ml+Oral+Solution+(Rosemont+Pharmaceuticals+Ltd)/, date accessed 03.02.2011 | Manfredi PL, Houde RW. Prescribing methadone, a unique analgesic. J Support Oncol 2003;1:216-220. | Nicholson, A.B. (2007). Methadone for cancer pain. Cochrane Databaseof Systematic Reviews, 3, CD003971.<br><br>Auret, K., Roger Goucke, C., Ilett, K.F., Page-Sharp, M., Boyd, F., &<br>Oh, T.E. (2006). Pharmacokinetics and pharmacodynamics of methadone enantiomers in hospice patients with cancer pain.<br>Therapeutic Drug Monitoring, 28(3), 359–366. | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | | | | American Pain Society. (2005). Guideline for the management of cancer pain in adults and children. Glenview, IL: Author.<br><br>Centeno, C., & Vara, F. (2005). Intermittent subcutaneous methadone administration in the management of cancer pain. Journal of Pain and Palliative Care Pharmacotherapy, 19(2), 7–12.<br><br>Moryl, N., Kogan, M., Comfort, C., & Obbens, E. (2005). Methadone in the treatment of pain and terminal delirium in advanced cancer patients. Palliative and Supportive Care, 3(4), 311–317. | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Health question 14: | What is the evidence to support the use of topical opioids in cancer pain? | | | | |
| Is question addressed? | Yes | No | No | No | No |
| Specific recommendation | There was insufficient evidence to support a recommendation. | - | - | - | - |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | | - | - | - |
| Health question 15: | What is the evidence to support the use of spinal opioids in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |

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| Specific recommendation | 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.<br><br>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. | Anaesthetic procedures- may be considered where:<br>• Conventional oral or parenteral therapies are proving unsuccessful<br>• Side-effects are intolerable<br>• A specific nerve block is likely to provide good analgesia, with minimal or acceptable side effects<br>• Expertise and support is available<br><br>Neuroaxial techniques (ie epidural or intrathecal) can be helpful in patients with neuropathic pain, ischaemic leg pain, incident pain and muscle spasticity. | The intrathecal route of opioid administration should be considered in patients with intolerable sedation, confusion, and/or inadequate pain control with systemic opioid administration. | No recommendation | Anaesthetic procedures may be considered where: conventional oral or parenteral therapies are proving unsuccessful side effects of medication are intolerable a specific nerve block is likely to provide good analgesia, with minimal or acceptable side effects expertise and support is available. |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Level of evidence | 4, 1-, 1+ | - | Greenberg HS, Taren J, Ensminger WD, Doan K. Benefit from and tolerance to continuous intrathecal infusion of morphine for intractable cancer pain. J Neurosurg 1982;57:360–364. | - | - |
| Source of recommendation (reference/ evidence) | Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002.;20:4040-9. | Scottish Intercollegiate Guidelines Network (SIGN) (2008) Control of pain in adults with cancer: A national clinical guideline, 7-9, Edinburgh: Scottish Intercollegiate Guidelines Network. www. sign.ac.uk/pdf/ SIGN106.pdf | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | Dahm P, Lundborg C, Janson M, Olegard C, Nitescu P. Comparison of 0.5% intrathecal bupivacaine with 0.5% intrathecal ropivacaine in the treatment of refractory cancer and noncancer pain conditions: results from a prospective, crossover, double-blind, randomized study. Regional Anesthes Pain Med 2000;25(5):480-7.<br><br>Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer (Cochrane Review). In The Cochrane Library Issue 1, 2005. Chichester; John Wiley. | | | | |
| Health question 16: | What is the evidence to support the use of different routes of administration for opioid treatment in the management of cancer pain? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | The oral route should be used for administration of opioids, if practical and feasible.<br><br>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.<br>In patients with stable pain who are unable to swallow oral medication transdermal administration of opioids should be considered. | Transdermal preparations should not be commenced in patients with uncontrolled pain or who are moribund. | The least invasive, easiest, and safest route of opioid administration should be provided to ensure adequate analgesia. Oral is the preferred route of administration for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences side-effects associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. | The oral route is preferred as it is the easiest, safest, and least invasive. Seven studies and the 2005 APS guidelines indicated that IV, subcutaneous (SC), oral transmucosal (OT), transdermal (TD), or rectal (PR) routes should be used in some cases. The intraspinal (IS) rout also may be appropriate | The oral route is the recommended route of administration and should be used where possible |
| Level of evidence | 3 | - | - | - | - |

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| Source of recommendation (reference/ evidence) | Nelson K, Glare P, Walsh D, ES G. A prospective, within-patient, crossover study of continuous intravenous and subcutaneous morphine for chronic cancer pain. J Pain Symptom Manage 1997;13(5):262-7. | SIGN 106 as baseline document | Bruera E, Kim HN. Cancer pain. JAMA 2003;290:2476–2479.<br><br>Portenoy RK, Lesage P. Management of cancer pain. Lancet 1999;353:1695–1700.<br><br>Stevens RA, Ghazi SM. Routes of opioid analgesic therapy in the management of cancer pain. Cancer Control 2000;7:132–141. | American Pain Society. (2005). Guideline for the management of cancer pain in adults and children. Glenview, IL: Author.<br><br>Koshy, R.C., Kuriakose, R., Sebastian, P., & Koshy, C. (2005). Continuous morphine infusions for cancer pain in resource-scarce environments: Comparison of the subcutaneous and intravenous routes of administration. Journal of Pain and Palliative Care Pharmacotherapy, 19(1), 27–33.<br><br>Mercadante, S., Arcuri, E., Fusco, F., Tirelli, W., Villari, P., Bussolino, C., et al. (2005). Randomized double-blind, double-dummy crossover clinical trial of oral tramadol versus rectal tramadol administration in opioid-naive cancer patients with pain. Supportive Care in Cancer, 13(9), 702–707. | - |

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| | | | | Elsner, F., Radbruch, L., Loick, G., Gartner, J., & Sabatowski, R. (2005). Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain. Journal of Palliative Medicine, 8(4), 743–750.<br><br>Weinbroum, A.A. (2005). Superiority of postoperative epidural over intravenous patient-controlled analgesia in orthopedic oncologic patients. Surgery, 138(5), 869–876. | |
| Health question 17: | What is the evidence to support the bioequivalence of opioids in a cancer pain setting? | | | | |
| Is question addressed? | Yes | No | No | No | No |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Specific recommendation | It is not possible to draw any firm conclusions about the equivalence or otherwise in clinical practice of different modified release morphine preparations.<br>• 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.<br>• Prescribers and pharmacists should ensure that patients understand any intended changes in the appearance of their medicine to ensure both adequate analgesia and safety. | - | - | - | - |
| Level of evidence | 1++ | | - | - | - |

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|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Wiffen P, Edwards J, McQuay H. Oral morphine for cancer pain (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley. | | - | - | - |
| Health question 19: | What is evidence for equianalgesic equivalencies in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | No | Yes |
| Specific recommendation | 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. Equianalgesic equivalencies provided | Caution should be used when converting opioids in opposite directions as potency ratios may be different. Where there is no direct conversion between opioids it is conventional practice to use Oral Morphine equivalents. Detail provided on indivudal drug conversions. | Guidance on prescribing oxycodone provided within algorithms | - | Equianalgesic equivalencies provided |
| Level of evidence | 4 | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Source of recommendation (reference/ evidence) | Twycross R, Wilcock A. Palliative care formulary. 3rd ed. London: Palliativedrugs.com; 2007.<br><br>Anderson R, Saiers J, Abram S, Schlicht C. Accuracy in equianalgesic dosing. conversion dilemmas. J Pain Symptom Manage 2001;21(5):397-406.<br><br>Patanwala A, Duby J, Waters D, Erstad B. Opioid conversions in acute care. Ann Pharmacother 2007;41(2):255-67.<br><br>Lehmann K, Zech D. Transdermal fentanyl: clinical pharmacology J Pain Symptom Manage 1992;7(3 suppl):8-16. | SIGN 106 baseline document | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| | An open, single dose, four part, randomised crossover study to compare the pharmacokinetics of oxycodone from an oxycodone injection 10mg/ ml administered as a subcutaneous, intravenous, or intramuscular bolus dose with an oxycodone normal release oral liquid 5mg/fml in 24 health male volunteers Napp Pharmaceuticals; 200? OXI1202 [unpublished]. | | | | |
| Health question 20: | What is the evidence to support the use of combination step 3 opioids in cancer pain? | | | | |
| Is question addressed? | No | No | No | No | No |
| Specific recommendation | - | - | - | - | - |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Health question 21: | What is the evidence for the management of cancer pain? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |
| Specific recommendation | Patients with moderate or severe breakthrough pain should receive breakthrough analgesia.<br><br>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.<br><br>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. | Every patient on regular opioids should have access to breakthrough analgesia which is traditionally approximately 1/6 (one sixth) of the total daily dose | Provide rescue doses of short-acting opioids for pain not relieved by extended-release opioids including breakthrough pain or acute exacerbations of pain, activity or position related pain, or pain at the end of dosing interval:<br>When possible, use the same opioid for short-acting and extended release forms.<br><br>Allow rescue doses of short-acting opioids of 10%–20% of 24-h oral dose (mg) every 1 h as needed. Ongoing need for repeated rescue doses may indicate a need for adjustment of regularly scheduled opioid dose. | For breakthrough pain, 10%–15% of the 24 hour total opioid dose should be available in an IR analgesic dosed at regular intervals. If breakthrough doses are required frequently or an end-of-dose failure occurs, the LA and breakthrough dose should be increased. The right dose is the one that provides the best relief and causes the fewest side effects | Every patient on regular opioids should have access to breakthrough analgesia which is traditionally approximately 1/6 (one sixth) of the total daily dose. A lower dose (one tenth is recommended in the BNF) may be adequate but this needs assessing on an individual basis.<br>Opioids are the "rescue medication" of choice in the management of breakthrough pain<br>• The dose of opioid "rescue medication" should be determined by individual titration<br>• Non-opioid analgesics may be useful in the management of breakthrough pain episodes. e.g. paracetamol, NSAIDs |

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| | | | Consider transmucosal fentanyl (lozenge, tablets, film) only in opioid tolerant patients for brief episodes of acute exacerbation of pain not attributed to inadequate dosing of around the clock opioid. Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids. Initiate transmucosal fentanyl with lowest dose (200-mcg lozenge or 100-mcg buccal tablet or 200-mcg buccal soluble film) and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)<br>Increase dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around the clock opioid fails to relieve pain at peak effect or at end of dose. | | • Interventional techniques may be useful in the management of breakthrough pain<br>• Non-pharmacological methods may be useful in the management of breakthrough pain episodes. |
| Level of evidence | Nil given; 4; 1- to 1++ | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Hanks G, Conno F, Cherny N, Hanna M, Kalso E, McQuay H, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Canc 2001;84(5):587-93.<br><br>Portenoy R. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 1999;79(2-3):303-12. | SIGN 106 baseline document | - | American Pain Society. (2005). Guideline for the management of cancer pain in adults and children. Glenview, IL: Author. | Bailey F, Farley A (2006) Oral opioid drugs In: Davies A (editor) Cancer-related Breakthrough Pain. Oxford: Oxford University Press. Pp 43–55.<br><br>Davies A N, Dickman A, Reid C, et al (2009) The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. European Journal of Pain. 13: 4: 331-8 |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | Farrar J, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst Monogr 1998;90(8):611-6.<br><br>Christie JM. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol 1998;16(10):3238-45. | | | | |

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| | Coluzzi PH, et al Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immedidate release (MSIR). Pain 2001;91(1-2):123-30.<br><br>Zeppetella G, Ribeiro M. Opioids for the management of breakthrough (episodic) pain in cancer patients (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley. | | | | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Health question 22: | What is the evidence to support best practice for opioid titration in cancer pain? | | | | |
| Is question addressed? | No | Yes | Partly | No | Yes |
| Specific recommendation | - | If pain control is inadequate, and there is no evidence of opioid toxicity, (i.e. hallucinations, myoclonic jerks, confusion, drowsiness) increase the regular and PRN dose by up to 30% (in exceptional cases a 50% increase may be appropriate). Continue to titrate up regular and PRN doses, (at 1/6 of the total daily dose), until adequate pain relief is achieved. | Guidance on titration provided within algorithms | - | Guidance on titration provided |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | |
| Health question 23: | What is the evidence to support opioid rotation / switching in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Yes | No | |

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| Specific recommendation | 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. | Alternative opioids may be considered if patients develop intolerable adverse effects with their current opioid without achieving adequate pain relief. This decision is optimally made in conjunction with specialist palliative care. | If opioid adverse effects are significant, an improved balance between analgesia and adverse effects might be achieved by changing to an equivalent dose of an alternative opioid | - | |
| Level of evidence | 2++ to 3 | - | - | - | - |
| Source of recommendation (reference/ evidence) | Mercadante S, Bruera E. Opioid switching: a systematic and critical review. Cancer Treat Rev 2006;32(4):304-15.<br><br>Riley J, Ross JR, Rutter D, Wells AU, Goller K, du Bois R, et al. No pain relief from morphine. Support Care Cancer 2006;14(1):56-64. | SIGN 106 as baseline document | - | | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
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| Health question 24: | What is the evidence to support best practice in the management of opioid toxicity/ overdose? | | | | |
| Is question addressed? | No | Yes | Yes | No | Yes |
| Specific recommendation | - | Any reversible precipitating cause should be treated e.g infection, deteriorating renal and/or hepatic function , hypercalcaemia. Symptoms and signs: Include drowsiness, myoclonic jerks, pinpoint pupils (poor discriminating sign), confusion/ agitation, hallucinations, vivid dreams, cognitive impairment and respiratory depression. Management<br>• Mild opioid toxicity: reduce the dose of opioid; ensure adequate hydration and treat any underlying cause. If agitation / confusion problematic haloperidol 1.5mg - 3 mg orally or subcutaneously can be given. | Assess for other causes of delirium (e.g., hypercalcemia, CNS, metastases, other psychoactive medications) If one cannot determine other possible causes of delirium, consider changing the opioid Consider nonopioid analgesic to allow reduction of the opioid dose Consider haloperidol, 0.5-2 mg PO or IV every 4-6 h; or olanzapine, 2.5-5 mg PO or sublingual every 6-8 h; or risperidone, 0.25-0.5 mg 1-2 times day | - | Any reversible precipitating cause should be treated. Mild opioid toxicity: reduce the dose of opioid; ensure adequate hydration and treat any underlying cause. If agitation/ confusion problematic haloperidol 1.5mg - 3 mg orally or subcutaneously can be given. |

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| | | • Moderate opioid toxicity: If respiratory rate ≥ 8/min, oxygen saturations are normal and patient not cyanosed and easily rousable discontinue regular opioid immediately and adopt a 'wait and see' approach. When pain recurs and toxicity resolves consider restarting at a reduced dose.<br>• Severe Opioid toxicity: If respiratory rate is 8/min or less, oxygen saturations are abnormal or the patient is cyanosed urgent hospital admission is indicated.<br>Consider reversal of respiratory depression using naloxone. Discontinue regular opioid immediately. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. The patient's background analgesia will subsequently need to be reviewed. | | | Moderate opioid toxicity: If respiratory rate ≥ 8/min, oxygen saturations are normal and patient not cyanosed and easily rousable, omit the next dose (or stop infusion/ remove patch) of regular opioid immediately and adopt a 'wait and see' approach. When the situation is more stable either omit or reduce further doses and re-assess pain before re-introduding regularly. Severe Opioid toxicity: If respiratory rate is 8/min or less, oxygen saturations are abnormal or the patient is cyanosed urgent hospital admission is indicated. Consider reversal of respiratory depression using naloxone. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. |

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| | | Seek specialist palliative medical advice for continuing problems- particularly if transdermal patches have been used. | | | The patient's background analgesia will subsequently need to be reviewed. Seek specialist palliative medical advice for continuing problems - particularly if transdermal patches have been used. |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | - |
| Health question 25: | What is the evidence to support the best practice in the management of opioid induce side effects (pruritis, nausea, constipation)? | | | | |
| Is question addressed? | Yes | Yes | Yes | Yes | Yes |

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| Specific recommendation | Patients commencing an opioid for moderate to severe pain should have access to a prophylactic antiemetic to be taken if required. | Patients receiving an opioid must have access to laxatives- usually a combination of stimulant and softener. If constipation persists despite optimal laxative dosing, consider opioids with less constipating effects such as fentanyl, or combined oxycodone-naloxone (Targinact®).<br><br>Nausea and vomiting: Patients commencing an opioid should have access to an antiemetic (e.g. cyclizine 50mg TDS, metoclopramide 10mg TDS or haloperidol 0.5-1.5mg nocte). Patients may develop tolerance to nausea in 5-7 days.<br><br>Sedation: Patients commencing opioids should be warned that mild sedation may occur for the first few days, and advised of the risks of driving or using machinery. | Opioid-induced bowel dysfunction should be anticipated and treated prophylactically with a stimulating laxative to increase bowel motility, with or without stool softeners as indicated.<br><br>Additional detail provided with guideline algorithms | A bowel regimen should be initiated concurrently with opioids to prevent constipation (e.g., stool softener, laxative)<br><br>Nausea may be controlled with prophylactic antiemetics until tolerance occurs (NCCN). Sedation usually resolves with tolerance. If it persists, the best approach is to reduce the opioid dose and increase the frequency. | Ensure regular laxatives are co-prescribed when prescribing opioids<br><br>All patients should have access to antiemetics when opioids are prescribed<br><br>Sedation: Patients commencing opioids should be warned that mild sedation may occur for the first few days, and advised of the risks of driving or using machinery<br><br>Dry mouth: All patients should be educated on the need for, and methods to achieve, good oral hygiene |

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| | | Dry mouth: All patients should be educated on the need for, and methods to achieve, good oral hygiene. Sugar free chewing gum can stimulate saliva and saliva substitutes or mouthwashes may be helpful. | | | |
| Level of evidence | Nil given | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed. Glenview, IL: American Pain Society; 2003.<br>Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. J Palliat Med 2008;11:575–581. | National Comprehensive Cancer Network. (2008). NCCN Clinical Practice Guidelines in OncologyTM: Adult cancer pain [v.1.2008]. Retrieved October 29, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf<br><br>American Pain Society. (2005). Guideline for the management of cancer pain in adults and children. Glenview, IL: Author. | - |

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| Health question 26: | What is the evidence to guide the use of opioids and management of cancer pain in patients with renal failure? | | | | |
| Is question addressed? | Yes | Yes | Yes | No | Yes |
| Specific recommendation | In patients with poor or deteriorating kidney function, the following are of considerable importance to prevent or manage toxicity:<br>• Choice of opioid<br>• Consideration of dose reduction and/or an increase in the dosage interval<br>• Change from modified release to an immediate release oral formulation<br>• Frequent clinical monitoring and review.<br><br>In the presence of reduced kidney function all opioids should be used with caution<br>• And at reduced doses and/or frequency. | Renal impairment of any degree can have a profound effect on the handling of many medicines and to ensure adequate pain management without significant side effects all analgesics should be carefully selected and titrated.<br><br>Specific detail provided on dosing of individual drugs. | Morphine should be avoided in patients with renal disease and hepatic insufficiency. | - | Opioids which do not have active metabolites (such as fentanyl) may be more suitable for patients in renal failure than morphine or diamorphine.<br><br>Oxycodone: In severe renal impairment (eGFR<10) start with small doses and slowly titrate up as accumulation can occur. |

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| | • 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 m2).<br>• Specialist palliative care advice should be sought for the appropriate choice, dosage and route of opioid in patients with reduced kidney function. | | | | |
| Level of evidence | 4 | - | - | . | - |
| Source of recommendation (reference/ evidence) | Broadbent A, Khor K, Heaney A. Palliation and chronic renal failure: Opioid and other palliative medications - Dosage guidelines. Progr Palliat Care 2003;11(4):183-90.<br><br>Mercadante S, Arcuri E. Opioids and renal function. J Pain 2004;5(1):2-19. | B roadbent A., Khor C., & Heaney A. (2003). Review. Palliation and chronic renal failure: opioid and other palliative medications – dosage guidelines. Progress in Palliative Care. 11:4:183-190 | - | . | Broadbent A (2003) Review: palliation and chronic renal failure: opioid and other palliative medications - dosage guidelines. Progress in Palliative Care. 11: 4:183-1901. Robson P (2004) The use of opioids in palliative care patients with renal failure. CME Cancer Medicine. 2: 2: 40-48 |

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| | Launay-Vacher V, Karie S, Fau JB, Izzedine H, Deray G. Treatment of pain in patients with renal insufficiency: The World Health Organization three-step ladder adapted. J Pain 2005;6(3):137-48.<br><br>Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage 2004; 28(5):497-504. | Davison, S. & Ferro, C. (2009). Management of pain in chronic kidney disease. Progress in Palliative Care. 17:4:186-195<br><br>Douglas C., Murtagh F., Chambers E., Howse M., & Ellershaw J. (2009). Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Palliative Medicine. 23:103-110 | | | |

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| | Pauli-Magnus C, Hofmann U, Mikus G, Kuhlmann U, Mettang T. Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. Nephrol Dialysis Transplant 1999;14(4):903-9.<br><br>Lee M, Leng M, Tiernan E. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. Palliat Med 2001;15(1):26-34. 181.<br><br>Babul N, Darke A, Hagen N. Hydromorphone metabolite accumulation in renal failure. J Pain Symptom Manage 1995;10(3):184-6. | | | | |

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| Health question 27: | What is the evidence to guide the use of opioids and management of cancer pain in patients with hepatic failure? | | | | |
| Is question addressed? | No | Yes | Yes | No | Yes |
| Specific recommendation | - | Prescribing for pain in liver disease can be complex and will depend on many factors with unpredictable outcomes in relation to drug clearance.<br>• Prescribing should be kept to a minimum where possible.<br>• For opioids, start with a low dose and titrate slowly according to response and side effects. Regular review is essential.<br>• A void transdermal and slow release preparations.<br>• Ensure patient is not constipated.<br>• Avoid known hepatotoxic drugs | Morphine should be avoided in patients with renal disease and hepatic insufficiency. | - | Prescribing for pain in liver disease can be complex and will depend on many factors with unpredictable outcomes in relation to drug clearance.<br><br>Prescribing should be kept to a minimum where possible.<br><br>For opioids, start with a low dose and titrate slowly according to response and side effects. Regular review is essential.<br><br>Avoid transdermal and slow release preparations.<br><br>Ensure patient is not constipated.<br><br>Avoid known hepatotoxic drugs. |
| Level of evidence | - | - | - | - | - |

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| Source of recommendation (reference/ evidence) | - | Davis M. Cholestasis and endogenous opioids. Liver disease and exogenous opioid pharmacokinetics. (2007) Clinical Pharmocokinetics. 46(10): 825-850 | - | - | Davis M (2007) Cholestasis and endogenous opioids. Liver disease and exogenous opioid pharmacokinetics. Clinical Pharmocokinetics. 46: 10: 825-850<br><br>Ford-Dunn S (2005) Managing patients with cancer and advanced liver disease. Palliative Medicine.19: 563-565<br><br>Gasche Y, Daali Y, Faithi M et al (2004) Codeine intoxication associated with ultrarapid CYP2D6 metabolism. New England Journal of Medicine. 351: 2827-2831 |

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| | | | | | Hand C, Sear J W, Uppington J et al.(1990) Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. British Journal of Anaesthesia. 64: 3: 276-82<br><br>Janssen-Cilag Ltd (2009) Durogesic patch: Summary of Product Characteristics: www.janssen.co.uk/ (accessed 18 January 2011)<br><br>Joint Formulary Committee (2010). British National Formulary. 59th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain |

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| | | | | | Morgan D, McLean A J (1995) Clinical pharmacokinetics and pharmacodynamic considerations in patients with liver disease an update. Clinical Pharmacokinetics. 29: 5: 370-91<br><br>Napp Pharmaceuticals Limited (2008) Oxycontin tablets: Summary of Product Characteristics. www.napp.co.uk/healthcarers (accessed 18 January 2011)<br><br>North-Lewis P, editor (2008) Drugs and the Liver. London: Pharmaceutical Press. pp75-99. |

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| | | | | | Pfizer Limited (2010) Ketalar injection: Summary of Product Characteristics. www.pfizer.co.uk/ (accessed 18 January 2011)<br><br>Pfizer Limited (2010) Lyrica capsules: Summary of Product Characteristics. www.pfizer.co.uk/ (accessed 18 January 2011)<br><br>Pfizer Limited (2010) Neurontin capsules: Summary of Product Characteristics. www.pfizer.co.uk/ (accessed 18 January 2011)<br><br>Rhee C, Broadbent A M (2007) Palliation and liver failure: palliative medication dosage guidelines. Journal of Palliative Medicine. 10: 3: 677-685 |

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| | | | | | Tegeder I, Lotsch J, Geisslinger G (1999) Pharamacokinetics of opioids in liver disease. Clinical Pharmacokinetics. 37: 17-40<br><br>Tweed J, Croxen F, Foot K (2008) Choice of analgesic. In North-Lewis P, editor. Drugs and the Liver. London: Pharmaceutical Press. pp171-210<br><br>Tweed, J. (2009) What Pharmacokinetic and Pharmacodynamic Factors Need to be Considered when Prescribing Drugs for Patients with Liver Disease. NELM. www.nelm.nhs.uk/en/categories/medicines-information (accessed 21/01/11)<br><br>Watson M, Lucas C, Hoy A et al (2009) Oxford Handbook of Palliative Care.2nd ed Oxford: O.U.P.pp71-2 |

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| Health question 28: | What is the best evidence to guide the management of cancer pain in patients who have a history of opioid dependence? | | | | |
| Is question addressed? | No | No | No | No | No |
| Specific recommendation | - | - | - | - | - |
| Level of evidence | - | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | - |
| Health question 29: | What is the evidence to support the addition of paracetamol to regular opioid in cancer pain? | | | | |
| Is question addressed? | Yes | No | No | No | No |
| Specific recommendation | Patients at all stages of the WHO analgesic ladder should be prescribed paracetamol and/ or a non-steroidal anti-inflammatory drug unless contraindicated. | - | - | - | - |
| Level of evidence | 1+ | - | - | - | - |

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|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Stockler M, Vardy J, Pillai A, Warr D. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. J Clin Oncol 2004;22(16):3389-94. | - | | - | - |
| Health question 30: | What is the evidence to support the use of NSAIDS in cancer pain? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | Patients at all stages of the WHO analgesic ladder should be prescribed paracetamol and/ or a non-steroidal anti-inflammatory drug unless contraindicated. | Step 1. For mild pain Regular prescription of non-opioid such as paracetamol and/or NSAID +/- an adjuvant | Guidance on NSAIDs provided within algorithms | Selective and nonselective NSAIDs can be used for mild to moderate acute and persistent cancer pain unless contraindicated | Patients with mild pain should receive either paracetamol +/- a NSAID at licensed doses. The choice should be based on a risk/benefit assessment for each individual patient. |
| Level of evidence | 1++ | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | McNicol E, Strassels S, Goudas L, Lau J, Carr D. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley. | McNichol E, Strassels S, Goudas L, Lau J, Carr D (2006) "NSAIDs or paracetamol, alone or combined with opioids, for cancer pain" Cochrane Review. The Cochrane Library Issue 1, Chichester; John Wiley.<br><br>Joint Formulary Committee (2007) British National Formulary. 55th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain. | - | National Comprehensive Cancer Network. (2008). NCCN Clinical Practice Guidelines in OncologyTM: Adult cancer pain [v.1.2008]. Retrieved October 29, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf<br><br>American Pain Society. (2005). Guideline for the management of cancer pain in adults and children. Glenview, IL: Author | McNicol ED, Strassels S, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD005180. DOI: 10.1002/14651858. CD005180 |
| Health question 31: | Is there any evidence to support the use of different routes of administration of NSAIDS in cancer pain? | | | | |
| Is question addressed? | No | No | No | No | No |
| Specific recommendation | - | - | - | - | - |
| Level of evidence | - | - | - | - | - |
| Health question 32: | What is the evidence to support the use of proton pump inhibitors as gastric protection when NSAIDs are prescribed in a cancer setting? | | | | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Is question addressed? | Yes | No | Yes | No | Yes |
| Specific recommendation | 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. | - | Well-tolerated proton pump inhibitors are recommended to reduce gastrointestinal side effects induced by NSAIDs. | - | Patients receiving a NSAID who are at risk of gastrointestinal side effects should be prescribed a proton pump inhibitor. |
| Level of evidence | 1++ | - | - | - | - |
| Source of recommendation (reference/ evidence) | Silverstein F, Graham D, Senior J, Davies H, Struthers B, Bittman R, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebocontrolled trial. Ann Int Med 1995;123(4):241-9. | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health question 33: | What is the evidence to support the use topical capsacin in cancer pain? | | No | | |
| Is question addressed? | Yes | Yes | - | No | Yes |
| Specific recommendation | - | None made | - | - | None made |
| Level of evidence | No evidence was identified for the use of capsaicin in patients with cancer pain. | - | - | - | - |
| Source of recommendation (reference/ evidence) | - | None identified | - | - | - |
| Health question 34: | What is the evidence to support the use of lidnocaine in a cancer setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | No evidence was identified for the use of lidocaine in patients with cancer pain. | Lidocaine 5% patches shown to be effective in the reduction of localised neuropathic pain. Start with the patch applied over the area of maximal pain for 12 hours, followed by a 12 hour patch free period. Application can be increased to 24 hours if tolerated. Up to 3 patches may be used at any one time. | Guidance on lidnocaine provided within algorithm | Topical lidocaine is a first line treatment for neuropathic cancer pain | Start with the patch applied over the area of maximal pain for 12 hours, followed by a 12 hour patch free period. Application can be increased to 24 hours if tolerated. Up to 3 patches may be used at any one time. |
| Level of evidence | - | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | - | Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M et al (2003) "Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomised, double-blind, placebo-controlled study" Pain , 106, 1-2, 151-8. | - | - | Meier T, Wasner G, Faust M et al (2003) Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomised, double-blind, placebo-controlled study. Pain. 106: 1-2: 151-8. |
| Health question 35: | What is the evidence to support the use of ketamine in a cancer setting? | | | | - |
| Is question addressed? | Yes | Yes | No | No | Yes |
| Specific recommendation | The use of ketamine as an analgesic should be supervised by a specialist in pain relief or a palliative medicine specialist. | Initiation and supervision should be restricted to palliative medicine or chronic pain specialist | - | - | Under specialist supervision only. |
| Level of evidence | 2++ to 4 | | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Bell, Eccleston, Kalso. Ketamine as an adjuvant to opioids for cancer pain (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley.<br><br>Yang C, Wong C, Chang J, Ho S. Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anesthes 1995;443(4):379-83. | Bell RF, Eccleston C, Kalso EA (2009) Ketamine as an adjuvant to opioids for cancer pain (Review) The Cochrane library 2009 issue 3 | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: A randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 2000;20(4):246-52.<br><br>Cerchietti LC, Navigante AH, Korte MW, Cohen AM, Quiroga PN, Villaamil EC, et al. Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. Pain 2003;105(1-2):265-73. | | | | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health question 36: | What is the evidence to support the use of anticonvulsants in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | 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. | It is recommended that patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant Careful monitoring of side effects should be observed. Specialist advice may be required. | Guidance on anticonvulsants provided within algorithms | When managing neuropathic pain, coanalgesics initially should be administered as a single agent, though some patients may require combinations from different coanalgesics categories<br><br>Anticonvulsants used in neuropathic pain include gabapentin, pregabalin, carbamazepine, oxycarbazapine, topiramate, sodium valproate, tiagabine, levetiracetam, and zonisimade | It is recommended that patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant Where neuropathic pain is difficult to control both groups of agents may be required. |
| Level of evidence | 1++ | - | - | | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Wiffen P, McQuay H, Edwards J, Moore R. Gabapentin for acute and chronic pain (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley.<br><br>Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain (Cochrane Review). In The Cochrane Library Issue 2, 2006. Chichester; John Wiley. | Wiffen P, McQuay H, Edwards J, Moore R (2006) Gabapentin for Acute and Chronic Pain, Cochrane Review. The Cochrane Library Issue 1, Chichester; John Wiley.<br><br>Siddall P, Cousins M, Otte A, Greising T, Chambers R, Murphy T (2006) "Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlles trial" Neurology, 67,10,1792-800 | - | Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., et al. (2007). Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain, 132(3), 237–251.<br><br>Dunteman, E.D. (2005). Levetiracetam as an adjunctive analgesic in neoplastic plexopathies: Case series and commentary. Journal of Pain and Palliative Care Pharmacotherapy, 19(1), 35–43. | National Institute for Health and Clinical Excellence (NICE) (2010) Neuropathic Pain: the pharmacological management of neuropathic pain in adults in non-specialist settings Clinical Guideline 96. London: National Institute for Clinical Excellence. www.nice.org.uk/guidance/CG96 (accessed 21 January 2011) |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health question 37: | What is the evidence to support the use of antidepressant in a cancer pain setting? | | | | - |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | 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. | It is recommended that patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant Careful monitoring of side effects should be observed. Specialist advice may be required. | Guidance on antidepressants provided within algorithms | When managing neuropathic pain, coanalgesics initially should be administered as a single agent, though some patients may require combinations from different coanalgesics categories. First-line treatments include certain antidepressants (i.e., tricyclic antidepressants [TCA] and dual reuptake inhibitors of serotonin and norepinephrine [SSNRI]. | It is recommended that patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant Where neuropathic pain is difficult to control both groups of agents may be required. |
| Level of evidence | 1+to 1++ | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Saarto T, Wiffen P. Antidepressants for neuropathic pain (Cochrane Review). In The Cochrane Library Issue 3, 2007.<br><br>Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain 2004;18(2):131-7.<br><br>Sindrup S, Bach F, Madsen C, Gram L, Jensen T. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 2003;60(8):1284-9. | 62 | - | Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., et al. (2007). Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain, 132(3), 237–251. | National Institute for Health and Clinical Excellence (NICE) (2010) Neuropathic Pain: the pharmacological management of neuropathic pain in adults in non-specialist settings Clinical Guideline 96. London: National Institute for Clinical Excellence. www.nice.org.uk/guidance/CG96 (accessed 21 January 2011)<br><br>Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005454. DOI: 10.1002/14651858.CD005454.pub2 |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S, Wernicke JF, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Pain 2005;116(1-2):109-18.<br><br>Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67(8):1411-20. | | | | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health question 38: | What is the evidence to support the use of benzodiazepines in a cancer pain setting? | | | | |
| Is question addressed? | No | Yes | No | No | Yes |
| Specific recommendation | - | Benzodiazepines (Clonazepam)<br>- Evidence for the efficacy for clonazepam is limited. It may be used alone or in combination with other neuropathic agents.<br>Starting dose – orally 0.25-0.5mg nocte, or via CSCI 0.5mg/24hrs. Sedation limits dose increases. | - | - | Evidence for the efficacy for clonazepam is limited. It may be used alone or in combination with other neuropathic agents |
| Level of evidence | - | - | | - | |
| Source of recommendation (reference/ evidence) | - | - | | - | |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Health question 39: | What is the evidence for the use of bisphosphonates in a cancer pain setting? | | | | |
| Is question addressed? | Yes | Yes | Partly | Yes | Yes |
| Specific recommendation | Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with metastatic bone disease. | There is evidence that they reduce the pain of bony metastases, especially associated with myeloma, prostate and breast carcinoma. They should not be first line therapy, but may be considered as part of a therapeutic regimen for treatment of metastatic bone pain | Guidance on bisphosphonates provided within algorithms | Bisphosphonates have been proven to provide some relief from bone metastasis; however, not enough evidence exists to recommend them as first-line treatment. Therefore, bisphosphonates are recommended when analgesics and/or radiotherapy are inadequate | They should not be first line therapy, but may be considered as part of a therapeutic regimen for treatment of metastatic bone pain. |
| Level of evidence | 1++ | - | - | - | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| Source of recommendation (reference/ evidence) | Wong J, Wiffen P. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley.<br><br>Carr DB, Goudas LC, Balk EM, Bloch R, Ioannidis JP, Lau J. Evidence report on the treatment of pain in cancer patients. J Natl Cancer Inst Monogr 2004;32:23-31. | Scottish Intercollegiate Guidelines Network (SIGN ) (2008) Control of pain in adults with cancer: A national clinical guideline, 7-9, Edinburgh: Scottish Intercollegiate Guidelines Network. www. sign.ac.uk/pdf/ SIGN106.pdf | - | Yuen, K.K., Shelley, M., Sze, W.M., Wilt, T., & Mason, M.D. (2006). Bisphosphonates for advanced prostate cancer. Cochrane Database of Systematic Reviews, 4, CD006250.<br><br>Wong, R., & Wiffen, P.J. (2002). Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database of Systematic Reviews, 2, CD002068. | - |

| | **Scottish Intercollegiate Guideline Network 106** (2) | **Guidelines and Audit Implementation Network** (73) | **National Comprehensive Cancer Network** (3) | **Oncology Nursing Society** (20) | **Palliative Adult Network Guidelines** (19) |
|---|---|---|---|---|---|
| | McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases (Cochrane Review). In The Cochrane Library Issue 2, 2000. Chichester; John Wiley. | | | | |
| Health question 40: | What is the evidence for the use of steroid medication in a cancer setting? | | | | |
| Is question addressed? | No | Yes | Partly | No | Yes |
| Specific recommendation | - | Corticosteroids may be used to treat cancer-related neuropathic pain but little evidence exists for their use. Suggested starting dose - dexamethasone 8mg mane for 3-5 days, then reduced to the minimum effective dose. If no significant improvement within 5 days then discontinue. | Guidance on steroids provided within algorithms | - | Suggested starting dose - dexamethasone 8mg mane for 3-5 days until a benefit is achieved, then reduced to the minimum effective dose. If no significant improvement within 5 days discontinue. |
| Level of evidence | - | | - | - | - |
| Source of recommendation (reference/ evidence) | - | - | - | - | - |

# Appendix V: Health questions

Literature searches on each of these health questions for the period between June 2007 and November 2011. The SIGN guideline 106 searches were completed in June 2007 and was therefore considered an appropriate starting point for the new searches. The European Palliative Care Research Collaborative (EPCRC, 2006-2010) performed a number of high level systematic reviews so as to inform the 2012 EAPC Cancer Pain Guidelines (21, 22). The EPCRC searches were of high quality and the 18 health questions that were addressed in these systematic reviews were not undertaken by the development group, leaving 22 health questions for investigation.

Due to the time lapse between completion of the guideline and signoff, a second literature search including all 40 health questions was undertaken in January 2015, for the time period 2011 to December 2014.

(**indicates health questions addressed in EPCRC searches*).

| | |
|---|---|
| **Pain and principles of pain management:** | |
| 1. | Is there any new evidence on pain assessment? |
| 2. | Is there any evidence that the use of pain assessment tools improves patient's pain scores? |
| 3. | Is there any evidence to support the association of cancer pain with psychological distress? |
| **Opioid Medication:** | |
| 4. | What is the evidence to support the use of tramadol in a cancer pain setting*? |
| 5. | What is the evidence to support the use of codeine in a cancer pain setting? |
| 6. | What is the evidence to support the use of tapentadol in a cancer pain setting? |
| 7. | What is the evidence to support the use of morphine in a cancer setting*? |
| 8. | What is the evidence to support the use of oxycodone in a cancer pain setting*? |
| 9. | What is the evidence to support the use of hydromorphone cancer pain setting*? |
| 10. | What is the evidence to support the use of fentanyl in a cancer pain setting? |
| 11. | What is the evidence to support the use of alfentanyl in a cancer pain setting? |
| 12. | What is the evidence to support the use of buprenorphine in a cancer pain setting? |
| 13. | What is the evidence to support the use of methadone in a cancer pain setting*? |
| 14. | What is the evidence to support the use of topical opioids in cancer pain? |
| 15. | What is the evidence to support the use of spinal opioids in a cancer pain setting*? |
| 16. | What is the evidence to support the use of different routes of administration for opioid treatment in the management of cancer pain*? |
| 17. | What is the evidence to support the bioequivalence of opioids in a cancer pain setting*? |
| 18. | What is evidence for equianalgesic equivalencies in a cancer pain setting*? |
| 19. | What is the evidence to support the use of opioid/opioid antagonist products in a cancer pain setting? |
| 20. | What is the evidence to support the use of combination step 3 opioids in cancer pain*? |
| **Opioids prescribing and side-effects: Specific patient populations:** | |
| 21. | What is the evidence for the management of cancer breakthrough pain*? |
| 22. | What is the evidence to support best practice for opioid titration in cancer pain*? |

| | |
|---|---|
| 23. | What is the evidence to support opioid rotation / switching in a cancer pain setting*? |
| 24. | What is the evidence to support best practice in the management of opioid toxicity/ overdose*? |
| 25. | What is the evidence to support the best practice in the management of opioid induce side effects (pruritis, nausea, constipation)*? |
| **Specific patient populations;** | |
| 26. | What is the evidence to guide the use of opioids and management of cancer pain in patients with renal failure? |
| 27. | What is the evidence to guide the use of opioids and management of cancer pain in patients with hepatic failure? |
| 28. | What is the best evidence to guide the management of cancer pain in patients who have a history of opioid dependence? |
| **Non opioid medication**; | |
| 29. | What is the evidence to support the addition of paracetamol to regular opioid in cancer pain? |
| 30. | What is the evidence to support the use of NSAIDS in cancer pain? |
| 31. | Is there any evidence to support the use of different routes of administration of NSAIDS in cancer pain? |
| 32. | What is the evidence to support the use of proton pump inhibitors as gastric protection when NSAIDs are prescribed in a cancer setting? |
| 33. | What is the evidence to support the use topical capsacin in cancer pain ? |
| 34. | What is the evidence to support the use of lidnocaine in a cancer setting? |
| 35. | What is the evidence to support the use of ketamine in a cancer setting? |
| 36. | What is the evidence to support the use of anticonvulsants in a cancer pain setting*? |
| 37. | What is the evidence to support the use of antidepressant in a cancer pain setting*? |
| 38. | What is the evidence to support the use of benzodiazepines in a cancer pain setting? |
| 39. | What is the evidence for the use of bisphosphonates in a cancer pain setting? |
| 40. | What is the evidence for the use of steroid medication in a cancer setting? |

# Appendix VI: Health questions; sample search chart

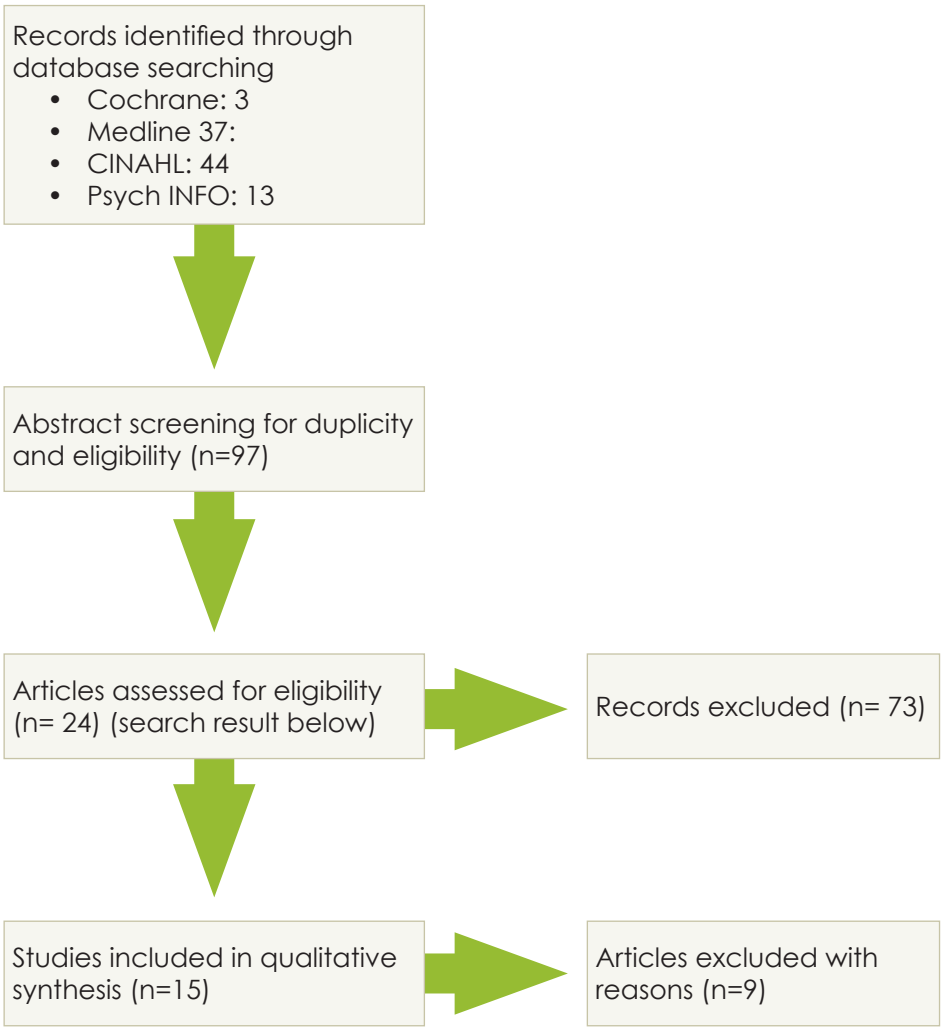
**Health question number 8**
What is the evidence to support the use of buprenorphine in a cancer pain setting?

**PICO format:**

**Population:** Adult cancer pain patients
**Intervention:** The use of Buprenorphine for the treatment of cancer pain.
**Comparison:** Patients on alternative opioid medications or placebo who have cancer pain.
**Outcome:** Change in pain and side effects of medication.

**Records identified through database searching**
Cochrane: 3
Medline: 37
CINAHL: 44
Psych INFO: 11

## Search Diagram



# Appendix VII: Summary PICO searches for Health Questions

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 1 and 2<br>1. Is there any new evidence on pain assessment*?<br>2. Is there any evidence that the use of pain assessment tools improves patients pain scores | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Pain assessment.<br>**Comparison:** Patients who do not have pain assessment.<br>**Outcome:** Pain scores<br>**Time** : N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cochrane<br>Medline<br>CINAHL<br>Psych INFO<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded n = 310<br>Included n =18<br><br>2011 - December 2014<br>Q1.<br>Excluded n = 459<br>Included n =19<br>Q2.<br>Excluded n = 464<br>Included n =0 |
| Q 3 Is there any evidence to support the association of cancer pain with psychological distress? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** No intervention but an association of psychological distress.<br>**Comparison:** Patients without cancer related pain.<br>**Outcome:** Not and outcome. An association<br>**Time** : N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Pubmed: 183<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded =180<br>Included = 3<br>2011 - December 2014<br>Excluded =273<br>Included = 5 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 4 What is the evidence to support the use of tramadol in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of tramadol<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores; safety<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded =34<br>Included = 8 |
| Q 5 What is the evidence to support the use of codeine in a cancer pain setting*? | **Population:** Adult patients with mild to moderate cancer pain directly due to cancer, who need regular analgesia<br>**Intervention:** Treatment with codeine<br>**Comparison:** placebo, other step 2 opioids, other analgesia (paracetamol, NSAIDS)<br>**Outcome:** 1. analgesic effect 2.safety, pt preference<br>**Time** : N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>CINAHL: 1 result, not relevant<br>PsychINFo: 5 results, nil relevant<br>MEDLINE: 4 results, nil relevant<br>Cochrane: 26 results for codeine, 1 relevant<br>Pubmed: 68 results, nil relevant<br>Uptodate: nil<br>NICE: nil<br>NHS evidence: nil<br><br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>No new publications/ recommendations available since SIGN 106<br>2011 - December 2014<br>Excluded = 24<br>Included = 8 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 6 What is the evidence to support the use of tapentadol in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** The use of tapentadol.<br>**Comparison:** Control groups/ placebo/ alternative analgesics.<br>**Outcome:** Pain scores<br>**Time** : N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cochrane: 0<br>Medline: 6<br>CINAHL: 7<br>Psych INFO:<br>Pub Med :6<br>(n =19)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 19<br>Included = 0<br>2011 - December 2014<br>Excluded = 47<br>Included = 8 |
| Q 7 What is the evidence to support the use of morphine in a cancer setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of morphine<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores;<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>*Dynamed*<br>*Up To Date*<br>*Pubmed*<br>*Sign*<br>*National Guideline Clearinghouse*<br>*Cochrane*<br>*Trip*<br>*Cinahl*<br>*Web of Science*<br>*Nice*<br>*Embase*<br>*GINA*<br>*Clinical Key*<br>*Google Scholar* | 2011 - December 2014<br>Excluded = 98<br>Included = 111 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 8 What is the evidence to support the use of oxycodone in a cancer pain setting*? | **Population:** Adult patients with Adult patients with pain directly due to cancer<br>**Intervention:** Treatment with Oxycodone<br>**Comparison**: Ptients who have not been given Oxycodone<br>**Outcome**: Effectiveness of Oxycodone in this setting<br>**Time**: N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>*Dynamed*<br>*Up To Date*<br>*Pubmed*<br>*Sign*<br>*National Guideline Clearinghouse*<br>*Cochrane*<br>*Trip*<br>*Cinahl*<br>*Web of Science*<br>*Nice*<br>*Embase*<br>*GINA*<br>*Clinical Key* | 2011 - December 2014<br>Excluded = 245<br>Included = 12 |
| Q 9 What is the evidence to support the use of hydromorphone cancer pain setting*? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of hydromorphone<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores;<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>*Dynamed*<br>*Up To Date*<br>*Pubmed*<br>*Sign*<br>*National Guideline Clearinghouse*<br>*Cochrane*<br>*Trip*<br>*Cinahl*<br>*Web of Science*<br>*Nice*<br>*Embase*<br>*GINA*<br>*Clinical Key* | 2011 - December 2014<br>Excluded = 69<br>Included = 10 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q10 What is the evidence to support the use of fentanyl in a cancer pain setting*?<br>1) What is the evidence showing that fentanyl is better than placebo, or other opioids in the management of pain in adult patients with moderate to severe cancer pain, never treated with strong opioids and requiring stable doses of opioids?***<br>2) What is the evidence showing that fentanyl is better than other opioids in the management of pain in adult patients with moderate to severe cancer pain, who are already on an opioid and require stable doses of opioid? | **Population:** Adult patients with moderate to severe cancer pain directly due to cancer, who need regular stable analgesia<br>1. never treated with strong opioid<br>2. treated with opioid<br>**Intervention:** Treatment with fentanyl (TD or SC/IV)<br>**Comparison**: Placebo, other opioids, other analgesia (paracetamol, NSAIDS)<br>Outcome: 1. analgesic effect<br>2. safety, pt preference<br>**Time**: N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>*Question 1) answered by Tassarini et al, Pall Medicine issue July 2011* excluded all related papers<br>Question 2)<br>CINAHL: 14 results, 9 relevant<br>PsychINFO: 15 results, 3 relevant<br>MEDLINE: 43 results, 14 relevant<br>Cochrane: 7 results, nil relevant<br>Pubmed: 100 results, 15 relevant (all duplicates from EBSCO results)<br>NICE: nil<br>NHS evidence: nil<br>(n =28)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 26<br>Included = 2<br>2011 - December 2014<br>Excluded = 83<br>Included = 6 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 11 What is the evidence to support the use of alfentanyl in a cancer pain setting*? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Pain assessment.<br>**Comparison**: Patients who do not have pain assessment.<br>**Outcome**: Pain scores<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cinahl+: 28<br>Pubmed: 162<br>EMBASE: 157<br>Cochrane: 56<br>(n = 403)<br><br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 396<br>Included = 7<br>2011 - December 2014<br>Excluded = 17<br>Included = 0 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 12 What is the evidence to support the use of buprenorphine in a cancer pain setting*? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** The use of Buprenorphine<br>**Comparison**: Placebo/ alternative analgesia/ alternative strong opioid medication.<br>**Outcome**: Pain scores/ pain outcomes<br>**Time:** n/a<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cochrane: 3<br>Medline: 37<br>CINAHL: 44<br>Psych INFO: 11<br>(n = 95)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 80<br>Included = 15<br>2011 - December 2014<br>Excluded = 105<br>Included = 16 |
| Q 13 What is the evidence to support the use of methadone in a cancer pain settting? | **Population** – Adult patients with cancer related pain<br>**Intervention** – methadone first line or rotated from other strong opioids<br>**Comparison** – other strong opioids or placebo<br>**Outcome** – pain scores and side effects<br>**Inclusion criteria** – adult patients with cancer related pain<br>**Exclusion criteria** – patients with chronic or non-malignant pain; children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 134<br>Included = 13 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 14 What is the evidence to support the use of topical opioids in cancer pain?<br>1) What is the evidence showing that topical (transcutaneous) opioids are better than placebo, or other topical treatments in the management of pain due to cancer in adult patients?<br>2) What is the evidence showing that topical (transcutaneous) opioids are better than placebo, or other oral analgesic treatments in the management of pain due to cancer in adult patients? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Treatment with topical opioids<br>**Comparison**: Placebo, other topical agents, other oral analgesia<br>**Outcome**:1. analgesic effect<br>2. safety, pt preference<br>**Time:** n/a<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>CINAHL: nil for opioid, topical, neoplasm. For opioid, topical: 13 results, 3 relevant<br>PsychINFO: 4 results, 2 relevant<br>MEDLINE: 56 results, 3 relevant<br>Cochrane: 3 results, 1 relevant (protocol only, not cancer specific)<br>Pubmed: 31 results, 7 relevant (1 duplicate with ebsco)<br>NHS evidence: 1 CRD review, based on LeBon/Zepetella review article<br>(n =108)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 92<br>Included = 14 + Cochrane + NHS CRD<br>2011 - December 2014<br>Excluded = 15<br>Included = 2 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 15 What is the evidence to support the use of spinal opioids in a cancer pain setting*? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of spinal opioids<br>**Comparison:** Control group/ placebo<br>**Outcome:** Pain scores; safety<br>**Time:** N/A<br>**Inclusion criteria:** Patients with cancer related pain.<br>**Exclusion Criteria:** Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 38<br>Included = 8 |
| Q16 What is the evidence to support the use of different routes of administration for opioid treatment in the management of cancer pain? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Treatment with Opioids (TD, SC, IV, PO , PR)<br>**Comparison:** Alternative routes of opioids, intranasal , buccal SL<br>**Outcome:** Analgesic effect<br>**Time:** N/a<br>**Inclusion criteria:** Patients with cancer related pain<br>**Exclusion Criteria:** Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 43<br>Included = 2 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 17 What is the evidence to support the bioequivalence of opioids in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Opioid bioequivalence studies<br>**Comparison:**<br>**Outcome:** Analgesic effect and side effects<br>**Time:** N/a<br>**Inclusion criteria:** Patients with cancer related pain<br>**Exclusion Criteria:** Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 32<br>Included = 1 |
| Q 18 What is evidence for equianalgesic equivalencies in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of opioids<br>**Comparison:** Alternative opioids<br>**Outcome:** Pain scores;<br>**Time:** N/A<br>**Inclusion criteria:** Patients with cancer related pain.<br>**Exclusion Criteria:** Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 15<br>Included = 4 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 19 What is the evidence to support the use of opioid/opioid antagonist products in a cancer pain setting? | **Population**: Adult cancer pain patients<br>**Intervention:** The use of opioids in combination with an opioid antagonist for cancer pain<br>**Comparison:** Patients on other analgesic medication or placebo who have cancer pain.<br>**Outcome:** Pain scores; safety<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cochrane: 27<br>Medline: 5<br>CINAHL: 4<br>Psych INFO: 1<br>Pubmed: 7<br>(n = 44)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 38<br>Included = 8<br>2011 - December 2014<br>Excluded = 20<br>Included = 3 |
| Q 20 What is the evidence to support the use of combination step 3 opioids in cancer pain? | **Population**: Adult cancer patients.<br>**Intervention**: The use of combination step 3 opioids.<br>**Comparison**: placebo/ opioid monotherapy.<br>**Outcome**: efficacy/ tolerability.<br>**Time:** N/a<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 27<br>Included = 1 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 21 What is the evidence for the management of cancer breakthrough pain? | **Population:** Adults patients with cancer related breakthrough pain<br>**Intervention:** The use of opioids for the management of cancer related breakthrough pain<br>**Comparison:** placebo or other opioids<br>**Outcome:** pain scores<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 121 Included = 12 |
| Q 22 What is the evidence to support best practice for opioid titration in cancer pain*? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Method of opioid titration<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores;<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | 2011 - December 2014<br>Excluded = 34<br>Included = 3 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 23 What is the evidence to support opioid rotation/switching in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Opioid rotation / switching for the management of opioid toxicity or refractory pain<br>**Comparison**: Control group<br>**Outcome**: Pain scores; safety; dependency<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain; and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 137<br>Included =10 |
| Q 24 What is the evidence to support best practice in the management of opioid toxicity/ overdose? What is the evidence to support best practice in the management of toxicity/overdose? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention** Management of opioid toxicity/overdose<br>**Comparison**: Control group<br>**Outcome**: Pain scores<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain; and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 78<br>Included = 1 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 25 What is the evidence to support the best practice in the management of opioid induce side effects (pruritis, nausea, constipation)? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Management of opioid side effects<br>**Comparison**:<br>**Outcome**: Best practice in management of opioid induced side effects<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 88<br>Included = 2 |
| Q 26 What is the evidence to guide the use of opioids and management of cancer pain in patients with renal failure? | **Population:** Adult patients with pain directly due to cancer and with renal failure<br>**Intervention:** management of cancer pain in patients with cancer and renal failure<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores; safety<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 48<br>Included = 3 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 27 What is the evidence to guide the use of opioids and management of cancer pain in patients with hepatic failure? | **Population:** Adult patients with pain directly due to cancer and with hepatic failure<br>**Intervention:** management of cancer pain in patients with cancer and hepatic failure<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores; safety<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 15<br>Included = 2 |
| Q 28 What is the best evidence to guide the management of cancer pain in patients who have a history of opioid dependence? | **Population:** Adults patients with opioid dependency who have cancer pain<br>**Intervention:** The use of opioids for the treatment of cancer pain in patients with opioid dependency.<br>**Comparison:** The use of opioids to treat cancer pain in patients without opioid dependency.<br>**Outcome:** Change in pain, opioid requirements and side effects of medication.<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>Cochrane: 14<br>Medline: 19<br>CINAHL: 15<br>Psych INFO: 25<br>Pubmed: 133<br>(n = 206)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 201<br>Included = 5<br>2011 - December 2014<br>Excluded = 46<br>Included = 7 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 29 What is the evidence to support the addition of paracetamol to regular opioid in cancer pain? | **Population:** Adult cancer pain patients.<br>**Intervention:** The use of paracetamol in addition to opioids in patients with cancer pain.<br>**Comparison:** The use opioids (without paracetamol) to treat cancer pain.<br>**Outcome:** Change in pain and opioid requirements.<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | June 2007 - November 2011<br>• Cochrane: 1<br>• Medline: 0<br>• CINAHL: 7<br>• Psych INFO: 0<br>• Pubmed: 7<br>(N= 16)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded =7<br>Included= 9<br><br>2011 - December 2014<br>Excluded =43<br>Included= 4 |
| Q 30 What is the evidence to support the use of NSAIDS in cancer pain*? | **Population:** adult patients with cancer pain **Intervention:** The use of NSAID for the treatment of cancer pain.<br>**Comparison**: Patients on other analgesic medication or placebo who have cancer pain.<br>**Outcome**: Change in pain and side effects of medication.<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: children | June 2007 - November 2011<br>Cochrane: 1<br>Medline: 6<br>CINAHL: 5<br>Psych INFO: 2<br>(n = 14)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded =13<br>Included= 1<br><br>2011 - December 2014<br>Excluded = 39<br>Included =2 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 31 Is there any evidence to support the use of different routes of administration of NSAIDS in cancer pain? | **Population:** adult patients with cancer pain **Intervention:** The use of different routes of administration of NSAID for the treatment of cancer pain.<br>**Comparison**: routes of administration of NSAIDs.<br>**Outcome**: Change in pain and side effects of medication.<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: children | See Q32 (duplicate)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>No new evidence identified |
| Q 32 What is the evidence to support the use of proton pump inhibitors as gastric protection when NSAIDs are prescribed in a cancer setting*? | **Population:** adult patients with pain directly due to cancer<br>**Intervention:** The co administration of Proton Pump inhibitors as gastric protection when using NSAID in a cancer setting (in this instance, also in a non-cancer setting due to limited evidence)<br>**Comparison**: Patients not taking PPIs.<br>**Outcome**: gastric complications/ ulceration incidence/ gastritis incidence/ nausea/ vomiting/ gastric irritation symptoms/ gastric haemorrhage.<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: children | June 2007 - November 2011<br>Cochrane: 0<br>Medline: 0<br>CINAHL: 60<br>Psych INFO: 0<br>Pubmed: 1<br>(n = 61)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 60<br>Included = 1<br><br>2011 - December 2014<br>Excluded = 84<br>Included = 5 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 33 What is the evidence to support the use topical capsacin in cancer pain *? | **Population:** adult patients with pain directly due to cancer<br>**Intervention:** the use of topical capsaicin for pain relief<br>**Comparison**: control group/ placebo<br>**Outcome**: Pain scores/ pain outcome **T**<br>**ime:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and Children | June 2007 - November 2011<br>Cinahl+: 121<br>Pubmed: 277<br>EMBASE: 112<br>Cochrane: 40<br>(n = 210)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 204<br>Included = 6<br><br>2011 - December 2014<br>Excluded = 28<br>Included = 3 |
| Q 34 What is the evidence to support the use of lidnocaine in a cancer setting? | **Population:** Adult cancer Pain Patients<br>**Intervention**: The use of lidocaine for the treatment of cancer pain.<br>**Comparison:** Patients on other analgesic medication or placebo who have cancer pain.<br>**Outcome:** Change in pain and side effects of medication.<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children | June 2007 - November 2011<br>Cochrane: 0<br>Medline: 6<br>CINAHL: 5<br>Psych INFO: 2<br>(N =13)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | June 2007 - November 2011<br>Excluded = 62<br>Included = 12<br><br>2011 - December 2014<br>Excluded = 69<br>Included = 8 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 35 What is the evidence to support the use of ketamine in a cancer setting*? | **Population**: Adult cancer Pain Patients<br>**Intervention**: The use of ketamine for the treatment of cancer pain.<br>**Comparison:** Patients on other analgesic medication or placebo who have cancer pain.<br>**Outcome:** Change in pain and side effects of medication.<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children | June 2007 - November 2011<br>Cochrane: 2<br>Medline: 9<br>CINAHL: 9<br>Psych INFO: 2<br>(n = 22)<br>2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 12<br>Included = 10<br><br>2011 - December 2014<br>Excluded = 54<br>Included = 14 |
| Q 36 What is the evidence to support the use of anticonvulsants in a cancer pain setting? | **Population:** Adult patients with pain directly due to cancer<br>**Intervention:** Use of anticonvulsants<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 57<br>Included = 8 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 37 What is the evidence to support the use of antidepressants in a cancer pain setting*? | **Population**: Adult patients with pain directly due to cancer<br>**Intervention**: Use of antidepressants<br>**Comparison**: Control group/ placebo<br>**Outcome**: Pain scores; safety<br>**Time**: N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: Patients with non-malignant or chronic non cancer pain and children. | 2011 - December 2014<br>Dynamed<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>GINA<br>Clinical Key | 2011 - December 2014<br>Excluded = 87<br>Included = 9 |
| Q 38 What is the evidence to support the use of benzodiazepines in a cancer pain setting? | **Population:** adult patients with pain directly due to cancer<br>**Intervention:** The use of benzodiazepines<br>**Comparison**: placebo/ alternative analgesics<br>**Outcome**: Pain scores<br>**Time:** N/A<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children | June 2007 - November 2011<br>Cinahl =3,735<br>Medline = 69,478<br>BioMedical Reference Collection = 2,563<br>( n = 102 potentially relevant)<br>2011 - December 2014<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 98<br>Included = 4<br><br>2011 - December 2014<br>Excluded = 103<br>Included =1 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 39 What is the evidence for the use of bisphosphonates in a cancer pain setting*? | **Population:** Adult cancer Pain Patients<br>**Intervention**: The use of bisphosphonates for the treatment of bone pain.<br>**Comparison**: Patients on other analgesic medication or placebo who have bone pain.<br>**Outcome**: Change in pain and side effects of medication.<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children | June 2007 - November 2011<br>Cochrane:43<br>Medline: 25<br>CINAHL: 28<br>Psych INFO: 10<br>Pubmed: 28<br>(n = 134)<br>2011 - December 2014<br>Up To Date<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Web of Science<br>Nice<br>Embase<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 134<br>Included = 18<br><br>2011 - December 2014<br>Excluded = 107<br>Included = 2 |

| Health Question | PICO | Databases searched | Articles excluded and included |
|---|---|---|---|
| Q 40 What is the evidence for the use of steroid medication in a cancer setting?<br>1) What is the evidence showing that steroids (oral/SC/IV), alone or as an adjunct, are useful in the management of pain directly due to cancer, in adult patients?<br>2) What is the evidence showing that dexamethasone (oral/SC/IV), alone or as an adjunct, is useful in the management of pain directly due to cancer, in adult patients?<br>3) What is the evidence showing that oral prednisolone, alone or as an adjunct, is useful in the management of pain directly due to cancer, in adult patients?<br>4) What is the evidence showing that hydrocortisone (oral/SC/IV) is useful in the management of pain directly due to cancer, in adult patients? | **Population:** adult patients with pain directly due to cancer, who may be on other analgesics<br>**Intervention:** treatment with steroid (dexamethasone, prednisolone, hydrocortisone)<br>**Comparison**: placebo, other analgesia<br>**Outcome:** 1. analgesic effect<br>2. safety<br>**Inclusion criteria**: Patients with cancer related pain.<br>**Exclusion Criteria**: patients with non-malignant or chronic non cancer pain and children<br>NOT use of steroids in spinal cord compression, raised intracranial pressure/ cerebral oedema, bowel obstruction, management of fatigue or anorexia.NOT intrathecal/intraarticular etc | June 2007 - November 2011<br>Cinahl: 2<br>PsychINFO: 4 (1 duplicate)<br>MEDLINE: 1 (duplicate)<br>Cochrane: 0<br>Pubmed:4 (duplicates)<br>NHS evidence: nil relevant<br>N= 5<br>2011 - December 2014<br>UpToDate<br>Pubmed<br>Sign<br>National Guideline Clearinghouse<br>Cochrane<br>Trip<br>Cinahl<br>Nice<br>Embase<br>Clinical Key<br>Google Scholar | June 2007 - November 2011<br>Excluded = 374<br>Included = 5<br><br>2011 - December 2014<br>Excluded = 266<br>Included = 5 |

# Appendix VIII Details of consultation process

The draft document was placed on the HSE National Clinical Programme for Palliative Care website for public consultation for a six week period in 2013.

Through the National Clinical Programme for Palliative Care Working Group and the RCPI Clinical Advisory Group, a broad and extensive consultation process was undertaken including professional organisations for health and social care professions and patient representative groups. All relevent stakeholders including the Health Information and Quality Authority and the Irish Cancer Society received a draft of the document with a covering letter requesting feedback and comment.

Individual and group responses were collected and collated in a tabular fashion noting changes to document based on suggestions received.The majority of suggestions related to formatting and terminology. No substantial changes were made to the document based on feedback. See table 20 below.

The National Clinical Programme for Radiology provided useful information regarding percutaneous cementoplasty for budget impact analysis which was considered in formulation of recommendation 41 and section 1.12 Resource implications.

The Programme was fortunate to have the guideline reviewed by two international experts: Professor Peter G Lawlor, Associate Professor, Division of Palliative Care, Department of Medicine, University of Ottawa, Clinical Investigator, Bruyère and Ottawa Hospital Research Institutes, Medical Director, Palliative Care Unit, Bruyère Continuing Care and Professor Mike Bennett, St. Gemma's Professor of Palliative Medicine, Academic Unit of Palliative CareLeeds Institute of Health Sciences, School of Medicine, University of Leeds. A summary of their review is included in table 21.

**Table 20** Respondents to the consultation process

| | |
|---|---|
| **Date** | July 2013 |
| **Patients and members of the public** | Public consultation on National Clinical Programme for Palliative Care HSE National Patient Advocacy Unit (August / September 2013) |
| **External review** | Professor Peter G Lawlor, Associate Professor, Division of Palliative Care, Department of Medicine, University of Ottawa, Clinical Investigator, Bruyère and Ottawa Hospital Research Institutes, Medical Director, Palliative Care Unit, Bruyère Continuing Care and Professor Mike Bennett, St. Gemma's Professor of Palliative Medicine, Academic Unit of Palliative Care, Leeds Institute of Health Sciences, School of Medicine, University of Leeds |
| **Clinical leaders and healthcare managers** | St Patrick's Hospital, Carrick on Shannon, Co. Leitrim,<br>Pharmacy Department, University Hospital Galway, HRB Clinical Research Facility, Galway<br>Carmel O'Donnell, Clinical Nurse Specialist, Letterkenny General Hospital<br>Dr Jane Fleming, Consultant in Palliative Medicine, Waterford Regional Hospital<br>Milford Care Centre<br>Dr Regina Codd, GP with The Community Oncology Team, The National Cancer Control Programme |
| **National committees/ organisations** | RCPI Clinical Advisory Group for the National Clinical Programme for Palliative Care<br>Marie Kehoe-O'Sullivan, Health Information and Quality Authority<br>Dr Michael Connolly, Head of Education, All Ireland Institute of Hospice and Palliative Care,<br>Dr Camillus K Power, Immediate Past Dean Faculty of Pain Medicine, College of Anaesthetists of Ireland,<br>Mary Ferns, Irish Cancer Society |
| **Professional groups** | Feedback channelled through representives on the National Clinical Programme for Palliative Care Working Group |

**Table 21** Summary Feedback and Response of those listed in Table 20

| **Recommendations: Validity, Understand ability and Presentation** | **Comment** | **Conclusion.** |
|---|---|---|
| • Queries raised grading of 'level of evidence' of recommendations with some reference to the fact that 'lack of evidence' does not automatically imply 'lack of efficacy' (although the sections on 'key finding' does help in this regard). | • The grading of evidence and recommendations is to reflects the international consensus model for grading as per the Oxford standards. | • No change to document |
| • It was suggested that a single conversion ratio for opioids should be mandated and used nationally. | • There is insufficient evidence to recommend one single conversion ratio for opioids. The function of the guideline is to present all relevant evidence to guide HCPs to formulate best decisions. | • No change to document. |
| • It was suggested that use of a limited number of anti-emetics should be mandated and used nationally for prophylaxis of opioid induced nausea | • There is insufficient evidence to recommend one anti emetic over another in the prophylaxis of opioid induced nausea. | • No change to document |
| • It was suggested that recommendation 3 could be combined with recommendation 1 | • Lacks in-depth evidence based psychological/ psychosocial management of pain. | • No change to document |
| • Document should not just be confined to pharmacological management of pain. | • The guideline is the pharmacological management of cancer pain. | • No change to document |
| • It was suggested that with regard to recommendation 3 a recommendation could be made on a specific tool for use nationally | • Currently, there is no consensus on a national patient reported tool or any other tool in palliative care | • No change to document.<br>• This will be considered when the guideline is reviewed. |
| • With regard to recommendation 8 it was suggested to highlight morphine as first line ( in terms of efficacy and economic benefits) | • There is no evidence to show that morphine or other step 3 opioids are more efficacious than each other. There is no recommendation based on economic factors. | • No change to document. |
| • A suggestion was made to provide a guideline for breakthrough in relation to butrans (Recommendation 14) | • The calculation of breakthrough dosing is one sixth of the 24 hour oral morphine equivalent by popular convention. This is stated in the document. | • No change to document. |

| General comments | Guideline Development Group feedback |
|---|---|
| There is an over-focus on the final chapter of life and perhaps insufficient consideration of cancer pain survivors and the problems that they may have in terms of pain management. | The scope of this guideline is dealing with pain in an active cancer setting and is not applicable to chronic, non-cancer pain. This would require a separate guideline. |
| Another important issue would be the appearance of cancer in patients who already have a persistent pain problem. Persistent pain affects 13% of the Irish population (Breivik et al 2006), so the chance of these patients getting cancer is quite high. | Acknowledged |
| There is an emphasis on the WHO analgesic ladder. The comments of the British Pain Society's cancer pain document which is referenced in the bibliography (381) which highlights the need for more emphasis on the bio psychosocial model over the WHO analgesic ladder particularly in the subgroups identified above. | The WHO analgesic ladder is still the primary model for the pharmacological management of cancer pain. There is not enough evidence or a well developed alternative model which the group could advocate nationally. |
| The expertise of the pain medicine community is often called in too late and therefore would support the concept of pain intervention as a fourth step in the ladder that needs timely consideration. | Agreed by the group in general. This guideline is about the pharmacological management of cancer pain. The GDG would welcome the opportunity to develop a model for enhanced pain medicine / anaesthetics / palliative care in the future. |
| In page 17 and 18, under the future research areas, perhaps you could include intrathecal drug delivery, neuromodulation and regional anaesthesia as areas of research | The guideline focuses on the pharmacological management of cancer pain and is not an interventional guideline. |
| On page 23 under types of pain, nociceptive pain, neuropathic pain, mixed pain, there is perhaps an omission - visceral (this is the international year of visceral pain - IASP), so this could be included as it is well recognised as a source of pain internationally. | Visceral pain is highlighted under nociceptive pain (page 25 and 26) and is in the diagram 1 as such. |

**Table 22** Thematic summary and response to external review

| |
|---|
| Section 1.10.2 the GDG added that development of an app for opioid dose conversions could facilitate implementation of the guideline.<br><br>The GDG upgraded the evidence level for recommendation 2 on the basis of the updated search and suggestion from the external review.<br><br>Recommendation 7 was amended based on new information from updated search and suggestion from the external review.<br><br>Recommendation 18.1 was reworded for clarity, on the suggestion of the external reviewer.<br>Section 2.2.1 amended on the suggestion of the external reviewer.<br><br>Section 2.4.1 updated on new information from updated search and suggestion from the external review.<br><br>Section 2.4.5 and recommendation 34 amended based on new information from updated search and suggestion from the external review. |

# Appendix IX: Budget impact assessment

## Economic impact report

**Key message**
Despite recognition of the significant cost burden associated with cancer pain, it remains difficult to quantify the economic impact that can be specifically attributed to the control of pain in cancer. As part of the preparation for this guideline, a formal search for evidence relating to the economic impact of cancer pain and the cost of treatment options was undertaken. There is very little comparative evidence; however, any evidence relevant to this guideline has been included.

The GDG considers that the literature provides insufficient evidence to quantify with a reasonable degree of certainty what impact the recommendations will have on resources nationally. Therefore, expert opinion guides the assessment of budget impact.

Where current practice complies with the recommendations there will be no resource implications. Implementation of the guideline may have resource implications at a local level if there is variation in clinical practice. Additional staff will not be required but additional training may be needed to ensure that personnel have the required knowledge and skills to support best practice.

It is possible that in time, improvements in assessment and management of cancer pain may offset any costs associated with implementation of the guideline. Therefore, the GDG encourages organisations to evaluate their own practices against the recommendations in this guideline and assess costs associated with implementation, locally. The resource effects to be considered at a local level are discussed in section 1.12.

**Best Practice Point: Pharmacoeconomics**
Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

## Economic search

### *Economic search Search methodology*

In the development of this guideline, a formal search for evidence relating to the economic impact of cancer pain and the cost of treatment options was undertaken. The following databases were searched for cost-effectiveness evidence according to the National Clinical Effectiveness Committee Guideline Developers Manual (2013).

- MEDLINE
- EMBASE
- Cochrane Database of Systematic Reviews (CDSR)
- NHS Economic Evaluation Database (NHS EED)
- Cochrane Database of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment Database (HTA)

### *Economic search Search strategy*

The first search was conducted in July 1st 2014. MEDLINE Search strategy is presented below. It was translated for use in each of the other databases. There were no date restrictions applied in any of the searches.

NHS EED Economic search filter was used (Centre for Reviews and Dissemination 2009)

**Table 23** Economic search filter

| ID | Search |
|---|---|
| | Exp "Neoplasms"/ |
| | Cancer* . ti,ab |
| | 1 or 2 |
| | Pain* N2 (cancer* or neoplas* or malignan* or tumor* OR tumour* or carcinoma* or sarcoma* or adenocarcinoma* or metasta* or blastoma* or lymphoma*).ti, ab |
| | Pain* .ti, ab |
| | "Pain Management"/ |
| | "Pain Measurement"/ |
| | Exp "Pain"/ |
| | 5 or 6 or 6 or 8 |
| | 3 and 9 |
| | 4 or 10 |
| | Palliat* .ti, ab |
| | "Palliative Care"/ |
| | Exp "Terminal Care"/ |
| | "Terminally Ill"/ |
| | 12 or 13 or 14 or 15 |
| | "Economics"/ |
| | Exp "Costs and Cost Analysis"/ |
| | Economics, Dental/ |
| | Exp "Economics, Hospital"/ |
| | Economics, Medical/ |
| | Economics, Nursing/ |
| | Economics, Pharmaceutical/ |
| | economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* .ti, ab |
| | (expenditure* not energy) .ti, ab |
| | value N1 money) . ti, ab |
| | budget*.ti, ab |
| | 17 or 18 or 19 or 20 or 21 or 21 or 22 or 23 or 24 or 25 or 26 or 27 |
| | (energy or oxygen) N cost. ti, ab |
| | (metabolic N cost). ti, ab |
| | (energy or oxygen) N expenditure. ti, ab |
| | 29 or 30 or 31 |
| | 28 not 32 |
| | Letter.pt |
| | Editorial.pt |

| ID | Search |
|---|---|
| | Historical article.pt |
| | Humans/ not Animals/ |
| | 34 or 35 or 36 or 37 |
| | 11 and 16 and 39 |
| | 33 not 38 |

The findings from the search are presented in Table 24 and Figure 3. 1,179 articles were retrieved. 402 eligible articles were identified but only 14 studies were suitable for inclusion in the qualitative synthesis. There was general agreement that pain is prevalent in the cancer population and costs of unrelieved pain are considered to be potentially very high. Despite this, it remains difficult to quantify the economic impact that can be specifically attributed to the control of pain in cancer both in Ireland and internationally. This is predominantly due to the paucity of rigorous studies conducted in the area. Additionally, only one study was conducted in Ireland, limiting generalizability to this country.

**Table 24** Ecomomic search results summary

| Database | Search Date | Results | Guideline Handbook NCEC for searching economic evidence |
|---|---|---|---|
| Medline | 8th July 2014 | Sensitive – 311 | NCEC (used NHS EED Economic Search Filter – Sensitivity) |
| Embase | 2nd July 2014 | Sensitive 864 | NCEC – Used NHS EED Economic Search filter |
| NHS EED | 7th July 2014 | 11 | NCEC<br>Used NHS EED Economic Search filter |
| DARE | 7th July 2014 | 0 | NCEC<br>Used NHS EED Economic Search filter |
| HTA | 7th July 2014 | 1 | NCEC<br>Used NHS EED Economic Search filter |
| Cochrane Central Register of Controlled Trials | 7th July 2014 | 39 | NCEC<br>Used NHS EED Economic Search filter |
| Cochrane Database of systematic reviews | 7th July 2014 | 4 | NCEC<br>Used NHS EED Economic Search filter |

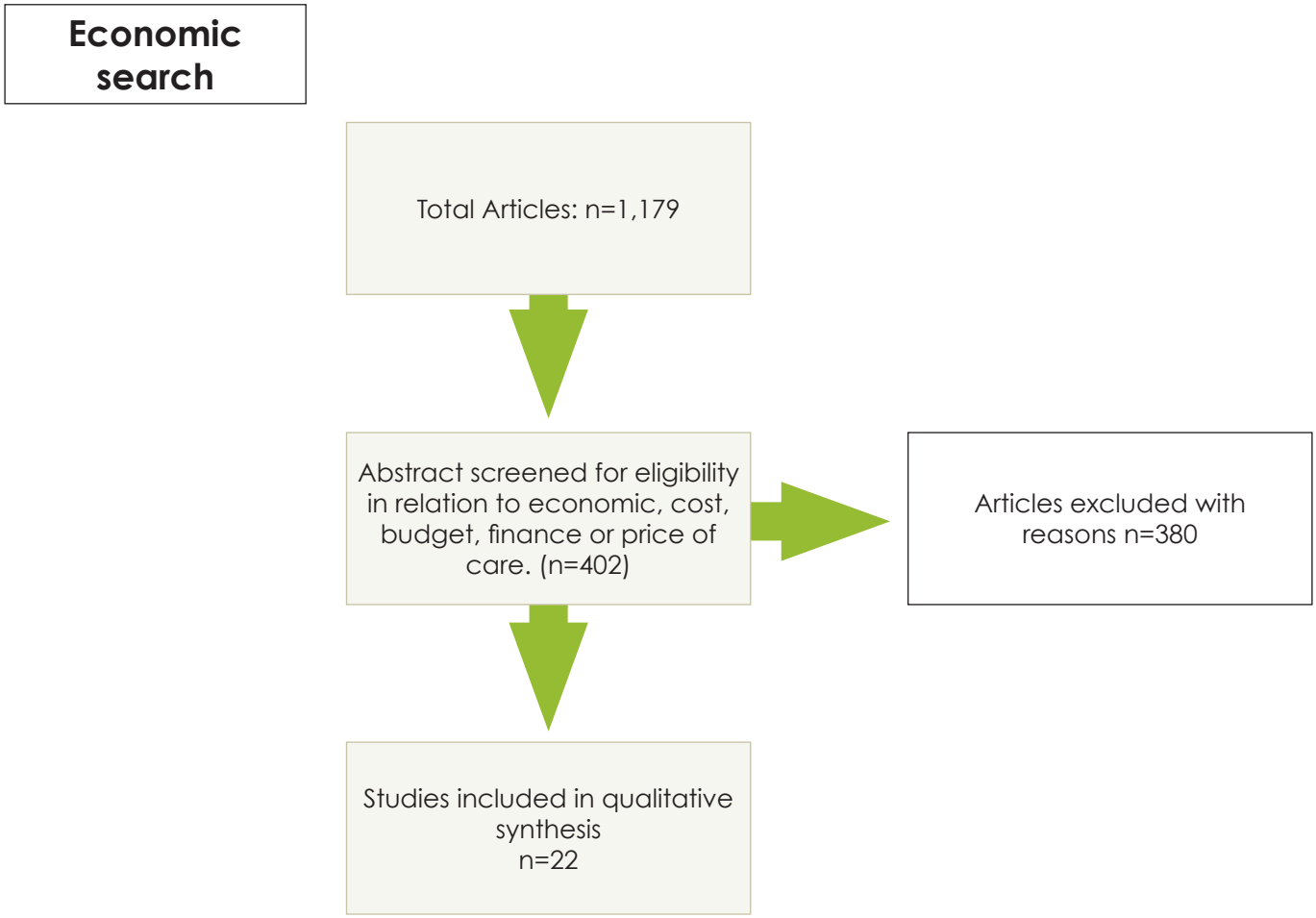



**Figure 3** Economic Search

**Table 25** Evidence table for economic search

| Study | Intervention | Analysis Details | Clinical & QALY Outcomes | Costs | Results |
|---|---|---|---|---|---|
| Abernethy et al. 2003 | Comparison of 3 different cancer pain management strategies.<br>1) guideline based care<br>2) oncology based care<br>3) usual care | Country: UK<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: 1 month<br>Model Type: CEA | Percentage of patients with effective cancer pain management 1) 80%, 2) 55%, 3) 30% | 1) €592<br>2) €477<br>3) €322 | ICER of 1) compared to 2) €463 per additional patient relieved of cancer pain<br>ICER of 2) compared to 3) €615 per additional patient relieved of cancer pain<br>ICER of 1) compared to 3) €538 |
| Chew et al. 2013 | Vertebroplasty for patients with spinal metastases.<br>1) metastatic disease<br>2) myeloma | Country: UK<br>Discount rate: None<br>Perspective: NHS<br>Time Horizon: LE 1) 8 months, 2) 20 months<br>Model Type: CUA | Median utility score increased on average for both groups from 0.421 pre-treatment to 0.5979 post-treatment. | Overall average cost of 1) and 2): €3080 per patient | Cost per QALY for 1) €81,704<br>Cost per QALY for 2) €32,759<br>The cost per QALY is derived from the mean cost and median survival time. |
| Fortner et al. 2003 | 1) Describe and 2) predict drivers of costs associated with pain for cancer patients | Country: US<br>Discount rate: None<br>Perspective: Societal<br>Time Horizon: 3 months<br>Model Type: Costing Study | A total of 373 cancer patients were sampled. Of those, 144 (39%) reported that they had experienced cancer-related pain and completed a questionnaire. The mean score for worst pain experienced in the past 24 hours was 4.4 (SD 2.2). | Mean pain-related costs during 3 month-period: €912 | Sixty-nine percent (69%) of the patients surveyed had experienced direct medical costs as a result of pain.<br>Fifty-seven percent (57%) reported incurring indirect costs related to pain.<br>Greater pain intensity, having breakthrough pain and interference from pain were strong predictors of direct and indirect costs. Age and lower income status were predictors of higher direct costs. |

| Study | Intervention | Analysis Details | Clinical & QALY Outcomes | Costs | Results |
|---|---|---|---|---|---|
| Gessner et al. 2000 | Total costs of formal care for patients with advanced cancer who received 1) 60 mg or 2) 90 mg of pamidronate in 6 cycles with intervals of 3 weeks. | Country: Switzerland<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: 11 months<br>Model type: Costing Study | After the first cycle, patients in both groups reported a 15% reduction in baseline pain scores. After the third and sixth cycles, patients with 1) reported a reduction of 22% and 36% and 2) 33% and 15% on baseline. | Differences in costs between 1) and 2) were not reported. The average cost per patient across both groups during the study was €23,836 (SD: €5,397). | Treatment with pamidronate reduced pain significantly but did not have a notable impact on total costs of formal care during the treatment or follow-up period. |
| Guest et al. 1998 | Patients with advanced cancer switched from weak to strong opioids | Country: UK<br>Discount rate: None<br>Perspective: NHS, voluntary and charitable sectors of palliative care<br>Time Horizon: LE 1) average <50 days, 2) average >100 days<br>Model Type: Costing Study | | Ranged from €4,547 to €7,038 | The duration of a patient's survival after switching to a stronger opioid, rather than the drug prescribed, determined total resource use. |
| Guest et al. 2005 | Patients with advanced cancer prescribed 1) 12-hourly sustained release (SR) morphine 2) Transdermal fentanyl monotherapy, 3) SR morphine plus 4-hourly morphine, 4) Transdermal fentanyl plus 4-hourly morphine | Country: UK<br>Discount rate: None<br>Perspective: NHS<br>Time Horizon: Lifetime<br>Model Type: Costing Study | | 1) €5,288 per patient,<br>2) €5,285 per patient,<br>3) €5,565 per patient,<br>4) €4,963; 71% of cost hospitalisation, 17% opioids | |
| Hanson et al 2008 | 1) Palliative care consultation for seriously-ill hospitalised patients 2) Matched controls with no palliative care consultation | Country: US<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: LOS> 4 days<br>Model Type: Costing Study | 1) showed improved mean symptom scores for pain, shortness of breath, and nausea between Day 1 and Day 3 compared to 2). The most significant improvement was in pain scores. | 1) had cost per day of €785 compared to 2) €878 | Referral to palliative care is often followed by decisions to forego costly interventions and improved symptom burden. Earlier referral results in increased cost-savings. |

| Study | Intervention | Analysis Details | Clinical & QALY Outcomes | Costs | Results |
|---|---|---|---|---|---|
| Mercadante et al. 2002 | 1) opioid escalation according to clinical needs<br>2) ketorolac 60mg/ daily orally in 3 doses and opioid escalation according to clinical needs | Country: Not reported<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: Lifetime<br>Model Type: Costing Study | 2) showed lower mean pain intensity compared to 1) after 1 week. Weekly follow-up found lower mean pain intensity for 1) relative to 2) for the remainder of the study period. | Daily costs similar in both groups | |
| Narayana et al. 2013 | To evaluate medical and pharmacy costs associated with breakthrough pain (BTP) in patients with advanced cancer. | Country: US<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: 1 year<br>Model Type: Costing Study | | Mean (SD) total annual health care costs for patients with and without BTP were €67,881 (€104,400) and €62,940 (€79,964), respectively.<br>Mean (SD) total annual pharmacy costs for patients with BTP were €16,223 (€28,593) versus €8,027 (€7,850) for patients without BTP. | Cancer patients in the survey group with controlled, persistent pain and BTP had higher total health care and pharmacy costs than cancer patients with controlled, persistent pain without BTP. |
| Pal et al. 2014 | 1) Hemi-body irradiation (HBI) for patients with extensive bone metastases compared with 2) oral morphine. | Country: India<br>Discount rate: None<br>Perspective: Societal<br>Time horizon: 6 months<br>Model type: Efficacy analysis | Reduced pain burden with 1) relative to 2) | Costs were not identified, however, greater efficacy of 1) was assumed to reduce medical resource use and results in cost saving relative to 2) | 1) was assumed to be cost-effective relative to 2) given the reduction in pain scores, medical and resource use and costs incurred by patients. |

| Study | Intervention | Analysis Details | Clinical & QALY Outcomes | Costs | Results |
|---|---|---|---|---|---|
| Ruggeri et al. 2014 | 1) Transnasal fentanyl citrate<br>2) morphine for the treatment of breakthrough pain in cancer patients | Country: Italy<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: 7 years<br>Model Type: CUA | QALY gain of 0.34 for 1) relative to 2) | 1) €7,156<br>2) €5,175 | ICER of 1) compared to 2) €8,159 per QALY. |
| Stam et al. 2009 | 1) intranasal fentanyl spray<br>2) oral fentanyl citrate for the treatment of breakthrough pain in cancer patients | Country: Sweden<br>Discount rate: None<br>Perspective: Payer<br>Time Horizon: LE (6 months)<br>Model Type: Efficacy analysis | QALY gain of 0.055 for 1) relative to 2) | Greater efficacy of 1) is assumed to reduce medical resource use and result in cost savings relative to 2) | 1) was assumed to be cost-effective relative to 2) given the increase in utility scores and lower formal care costs. |
| van den hout et al. 2003 | 1) Single- or 2) multiple-fraction radiotherapy in patients with painful bone metastases | Country: The Netherlands<br>Discount rate: None<br>Perspective: Societal<br>Time Horizon: Lifetime<br>Model Type: CUA | No differences were found in life expectancy or quality adjusted life expectancy between 1) and 2). | Direct costs were higher for 2) €3,884 relative to 1) €2,859. The difference in societal costs were also higher for 2) €7,568 compared with 1) €5,512, but this was not statistically significant at the 95% level. | For willingness-to-pay between €5115 and €40,927 per QALY, 1) was cost-effective relative ($P \leq .05$) to 2). Overall, 1) provides equal palliation and quality of life relative to 2) and has lower medical and societal costs in The Netherlands. |

# Appendix X: Feedback from Medicines Management Programme

Comments approved by Prof. Michael Barry, MMP Clinical Lead, 1/4/2014.
**Pharmacological Management of Cancer Pain in Adults**
Aug 2013

**Suggestions:**

**2.3.1.2 Opioids for moderate to severe pain sub heading Methadone**
From an MMP point of view, is it possible to mention cost as a consideration seeing as all the listed drugs demonstrate equivalent efficacy and tolerability and all are valid choices as first and subsequent choices (morphine sulphate, oxycodone, hydromorphone anyway, not including methadone as it's for specialist use in this setting)
Is it possible to recommend using the most cost effective option as first line, when no other contraindications?

**2.3.3. Opioid side-effects sub heading constipation**
No specific laxative mentioned for constipation. Again is it possible to make reference to choosing a cost effective agent as first line? Again, perhaps a mention of cost here?

**2.4.3.2 Evidence in non-cancer pain**
Recommendation 32: As it is mentioned earlier that pregabalin less than 150mg daily was not found to be effective should the recommendation read "There is evidence to support the use of anti-epileptics, such as gabapentin and pregabalin, at suitable doses, for the treatment of neuropathic pain." First line choice should be based on most cost effective agent (gabapentin would currently be much more cost effective than pregabalin).

**Section 2.4.4**
Should it be mentioned at the start of each section what the drug is actually licensed for (as is done for Versatis®). If recommending for an unlicensed indication, should we state that at the start?

**Action:**
The feedback informed a "Best Practice Point: Pharmacoeconomics" which was added to section 1.12, 2.3.1.2 and Appendix IX.

# Appendix XI: Glossary of abbreviations

| Abbreviation | Meaning |
|---|---|
| 3DS | Three day switch (methadone conversion) |
| ADAPTE | The ADAPTE Collaboration is an international collaboration of researchers, guideline developers, and guideline implementers who aim to promote the development and use of clinical practice guidelines through the adaptation of existing guidelines |
| AGREE 11 | Appraisal of Guidelines for Research and Evaluation II |
| BD | Twice daily |
| BPI | Brief pain inventory |
| BTP | Breakthrough pain |
| CDSR | Cochrane Database of Systematic Reviews |
| CEA | Cost Effectiveness Analysis |
| CEBM | Centre for Evidence Based Medicine |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CEO | Chief Executive Officer |
| CHM | Commission on human medicines |
| CKD | Chronic kidney disease |
| COX | Cyclo-oxygenase (COX-1/COX-2) |
| CR | Controlled release |
| CrCl | Creatinine clearance |
| CSCI | Continuous subcutaneous infusion |
| CUA | Cost-utility analysis |
| CYP 2D6 | Cytochrome P2D6 |
| CYP 3A4 | Cytochrome P450 3A4 |
| DARE | Cochrane Database of Reviews of Effects |
| DRG | Diagnosis Related Group |
| DSM | Diagnostic and statistical manual of mental disorders. (American Psychiatric Association.) |
| EAPC | European Association of Palliative Care |
| eGFR | Estimated glomerular filtration rate |
| EORTC | European Organization for Research and Treatment of Cancer |
| EPCRC | European Palliative Care Research Collaboration |
| ER | Extended release |
| ESAS | Edmonton Symptom Assessment Scale |
| ESMO | European Society of Medical Oncology |
| GAIN | Guidelines and Audit Implementation Network |
| GDG | Guideline Development Group |
| GI | Gastrointestinal |
| GP | General Practitioner |
| H3G | Hydromorphone-3-glucuronide |
| HADS | Hospital Anxiety and Depression Scale |
| HBI | Hemi-body irradiation |
| HIQA | Health Information and Quality Authority |
| HIPE | Hospital In-Patient Enquiry |
| Hr | Hour |
| HRB | Health Research Board |
| HSE | Health Services Executive |

| Abbreviation | Meaning |
|---|---|
| HTA | Health Technology Assessment |
| IASP | International Association for the Study of Pain |
| ICER | Incremental Cost Effectiveness Ratio |
| ICT | Information and communications technology |
| ICV | Intracerebroventricular |
| IR | Immediate Release |
| IS | Intraspinal |
| IV | Intravenous |
| JAMA | Journal of the American Association |
| M3G | Morphine-3-glucuronide |
| M6G | Morphine-6-glucuronide |
| mcg | Micrograms |
| MDT | Multidisciplinary team |
| MELD score | Model for End-Stage Liver Disease score |
| MF | Multiple fraction (radiation) |
| mg | Milligrams |
| MI | Myocardial infarction |
| mmol/L | Millimoles per litre |
| MMT | Methadone maintenance therapy |
| MR | Modified release |
| MSIR | Morphine sulfate immedidate release |
| NCCN | National Comprehensive Cancer Network |
| NCEC | National Clinical Effectiveness Committee |
| NCPPC | National Clinical Programme Palliative Care |
| NeLM | NHS National Electronic Library For Medicines |
| NHS | National Health Service |
| NHS EED | NHS Economic Evaluation Database |
| NICE | National Institute for Health and Care Excellence |
| NMDA | N-methyl-D-aspartate |
| NNH | Numbers needed to harm |
| NNT | Numbers Needed to Treat |
| NPIS | Numeric Pain Intensity Scale |
| NRS | Numeric rating scales |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| Od | Once daily |
| ONJ | Osteonecrosis of the jaw |
| OT | Oral transmucosal |
| OTFC | Oral transmucosal fentanyl citrate |
| PACSLAC | Pain Assessment Checklist for Seniors with Limited Ability to Communicate |
| PANG | Palliative Adult Network Guidelines |
| PAS | Patient Access Scheme(s) NHS |
| PICO | Population/patient; intervention; comparison/control; outcome |
| PHN | Post herpetic neuralgia |
| PO | By mouth |
| POMS | Profile of Mood States |
| POS | Palliative Outcome Scale |

| Abbreviation | Meaning |
|---|---|
| PPI | Proton pump inhibitor |
| PR | By rectum |
| PRN | Pro re nata (as required) |
| PTSS | Pain Treatment Satisfaction Scale |
| QALY | Quality-Adjusted-Life-Year |
| QoL | Quality of Life |
| RANKL | Receptor activator of nuclear factor kappa-B ligand |
| RCT | Randomised controlled trial |
| RCPI | Royal College of Physicians of Ireland |
| RI | Renal impairment |
| SAG | Stop and go (methadone conversion) |
| SC | Subcutaneous |
| SD | Standard deviation |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SNRI | Serotonin and noradrenalin reuptake inhibitor |
| SF | Single fraction (radiation) |
| SPC | Summary of Product Characteristics |
| SR | Sustained release |
| SRE | Skeletal-related events |
| SSRI | Selective serotonin reuptake inhibitors |
| STAS | Support Team Assessment Schedule |
| TCA | Tricyclic antidepressant |
| TD | Transdermal |
| TDS | Three times a day |
| TENS | Transcutaneous electrical nerve stimulation |
| TMD | Total Mood Disturbance |
| TSE | Transcutaneous spinal electroanalgesia |
| UK | United Kingdom |
| UL | University of Limerick |
| US | United States |
| VAS | Visual analogue scale |
| VRS | Verbal rating scales |
| WHO | World Health Organisation |

# Appendix XII: The Edmonton Symptom Assessment scale[3]

Capital Health

CARITAS HEALTH GROUP

**Edmonton Symptom Assessment System: Numerical Scale**
Regional Palliative Care Program

**Please circle the number that best describes:**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible pain |
| Not tired | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible tiredness |
| Not nauseated | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible nausea |
| Not depressed | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible depression |
| Not anxious | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible anxiety |
| Not drowsy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible drowsiness |
| Best appetite | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible appetite |
| Best feeling of wellbeing | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible feeling of wellbeing |
| Not shortness of breath | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible shortness of breath |
| Other problem | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |

Patients Name _____

Date _____ Time _____

Complete by (check one)

- ❑ Patient
- ❑ Caregiver
- ❑ Caregiver assisted

***BODY DIAGRAM ON REVERSE SIDE***

3 1. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multi-centre comparison of two numerical versions of the Edmonton Symptom Assessment System in palliative care patients J Pain Symptom Manage 2011; 41:456-468.
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# Appendix XIII: The Palliative Outcome Scale (POS): Patient Version

**Patient Outcome Scale**[4]

## PATIENT QUESTIONNAIRE (version 2)

www.pos-pal.org

Patient name: ..... Assessment date: .....

Date of birth: ..... Assessment no: .....

Care setting: .....

Please answer the following questions by ticking the box next to the answer that is most true for you. Your answers will help us to keep improving your care and the care of others.
Thank you.

**1 Over the past 3 days, have you been affected by pain?**

- ❑ 0 Not at all, no effect
- ❑ 1 Slightly - but not bothered to be rid of it
- ❑ 2 Moderately - pain limits some activity
- ❑ 3 Severely - activities or concentration markedly affected
- ❑ 4 Overwhelmingly - unable to think of anything else

**2 Over the past 3 days, have other symptoms e.g. nausea, coughing or constipation seemed to be affecting how you feel?**

- ❑ 0 No, not at all
- ❑ 1 Slightly
- ❑ 2 Moderately
- ❑ 3 Severely
- ❑ 4 Overwhelmingly

**3 Over the past 3 days, have you been feeling anxious or worried about your illness or treatment?**

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes - affects my concentration now and then
- ❑ 3 Most of the time - often affects my concentration
- ❑ 4 Can't think of anything else - completely pre-occupied by worry and anxiety

4 **Palliative Outcome Scale** - http://pos-pal.org/maix/terms-and-conditions.php
POS is copyright. License for use of any version of POS is granted free of charge. However you may not charge for use of POS. If you provide POS to others you must ensure that they register and adhere to these conditions.

**4 Over the past 3 days, have any of your family or friends been anxious or worried about you?**

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes – it seems to affect their concentration
- ❑ 3 Most of the time
- ❑ 4 Yes, always preoccupied with worry about me

**5 Over the past 3 days, how much information have you and your family or friends been given?**

- ❑ 0 Full information or as much as wanted – always feel free to ask
- ❑ 1 Information given but hard to understand
- ❑ 0 Information given on request but would have liked more
- ❑ 3 Very little given and some questions were avoided
- ❑ 4 None at all – when we wanted information

**6 Over the past 3 days, have you been able to share how you are feeling with your family or friends?**

- ❑ 0 Yes, as much as I wanted to
- ❑ 1 Most of the time
- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all with anyone

**7 Over the past 3 days, have you been feeling depressed?**

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes
- ❑ 3 Most of the time
- ❑ 4 Yes, all the time

If you have placed a tick in boxes 3 or 4 for this question, please speak with your nurse or doctor at your next appointment.

**8 Over the past 3 days, have you felt good about yourself as a person?**

- ❑ 0 Yes, all the time
- ❑ 1 Most of the time
- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all

**9 Over the past 3 days, how much time do you feel has been wasted on appointments relating to your healthcare, e.g. waiting around for transport or repeating tests?**

- ❑ 0 None at all
- ❑ 2 Up to half a day wasted
- ❑ 4 More than half a day wasted

**10 Over the past 3 days, have any practical matters resulting from your illness, either financial or personal, been addressed?**

- ❑ 0 Practical problems have been addressed and my affairs are as up to date as I would wish
- ❑ 2 Practical problems are in the process of being addressed
- ❑ 4 Practical problems exist which were not addressed
- ❑ 0 I have had had no practical problems

**11 If any, what have been your main problems in the last 3 days?**

1. .....

2. .....

**12 How did you complete this questionnaire?**

- ❑ 0 On my own
- ❑ 1 With the help of a friend or relative
- ❑ 2 With the help from a member of staff

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