WHO Guidelines for the Pharmacologic and Radio-therapeutic Management of Cancer Pain in Adults and Adolescents

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Introduction

Cancers are among the leading causes of morbidity and mortality worldwide, responsible for 8.8 million deaths in 2015. Annual cancer cases are expected to rise from 14 million in 2012 to 22 million before 2032, significantly increasing the burden on patients, families, communities and the health system.[1] Pain is experienced by 55% of patients undergoing anti-cancer treatment and by 66% of patients who have advanced, metastatic, or terminal disease.[2]

The goal of cancer pain management is to relieve pain to a level that allows for an acceptable quality of life. The World Health Organization (WHO) *Guidelines for the Pharmacologic and Radio-therapeutic Management of Cancer Pain in Adults and Adolescents* are intended to provide evidence-based guidance to healthcare providers on appropriate approaches to initiating and managing cancer pain in adolescents and adults, including the older person. The guidelines can act as the basis for national guidelines and for the inclusion of cancer pain management and care in primary health care programmes, using a person-centred and integrated approach.

Aims of the guidelines

1. To provide management guidance to healthcare providers (i.e. the end-users of these guidelines: physicians, nurses, pharmacists, and caregivers) on the adequate relief of pain associated with cancer or its treatment in adults and adolescents.

2. To assist policy-makers, programme managers, and public health personnel to create and facilitate appropriately balanced policies on opioids and prescribing regulations for effective and safe cancer pain management.

Scope of the guidelines

The scope of these guidelines includes medical and radio-therapeutic management of cancer pain. Anaesthetic, psychological, social, spiritual, physiotherapeutic, and surgical modes of cancer pain management are integral to comprehensive cancer pain management, and are discussed in this document, but are outside the scope of these guidelines.

The clinical guidelines and recommendations document is organized into three focal areas:

I. Analgesia of Cancer Pain: This addresses choice of analgesic medicine when initiating pain relief and choice of opioid for maintenance of pain relief, including optimization of rescue medication, route of administration, and opioid rotation and cessation
II. Adjuvant medicines for Cancer Pain: This includes use of steroids, anti-depressants and anti-convulsants as adjuvant medicines
III. Management of pain related to bone metastases: This incorporates use of bisphosphonates and fractionated radiotherapy to manage bone metastases

Following on publication of the guidelines, a series of subsidiary products will be developed that will address service delivery aspects of implementation, including WHO guidance on cancer pain assessment.

Guidelines process and decision-making

The process followed in the development of these guidelines is outlined in the WHO Handbook for Guideline Development and involved: (1) recruitment of the Guideline Development Group (GDG); (2) declaration of interest by GDG members and peer reviewers; (3) identification, appraisal and synthesis of available evidence; (4) formulation of recommendations with inputs from a wide range of stakeholders; and (5) preparation of documents and plans for dissemination.

The GDG is an international group of experts representing the various WHO Regions. The scope of the guidelines and questions were defined in consensus with the GDG members on 28th and 29th July 2016. A total of 13 clinical questions were formulated by the GDG and the Steering Group with inputs from external reviewers. A series of systematic reviews was conducted across multiple databases for each critical question and GRADE Evidence Profiles were prepared.

The recommendations were formulated by the GDG, during a face-to-face meeting at WHO headquarters in Geneva, 20 – 21 November, 2017. The WHO provided technical and administrative support. The quality of the supporting evidence was graded as high, moderate, low and very low using GRADE methodology. The GDG members discussed the evidence, clarified points, and interpreted the findings in order to develop recommendations. The GDG considered the relevance of the recommendations for patients with cancer pain considering the balance of benefit and harm of each intervention; values and preferences of patients; costs and resource use; and other relevant practical issues for providers in low- and middle-income countries.

Recommendations were made for individual interventions, but the GDG recognizes that these interventions are best implemented as part of an integrated care plan, including comprehensive pain assessment prior to initiating pain relief and ongoing monitoring of pain with adjustments made to dosage and choice of medicine as necessary.

List of Recommendations

Analgesia for cancer pain	
Initiation of pain relief	*Recommendation* In adults (including older persons) and adolescents with pain related to cancer, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids should be used at the stage of initiation of pain management, either alone or in combination, depending on clinical assessment and pain severity in order to achieve rapid, effective and safe pain control. *(Strong recommendation; low quality evidence)* Remarks ✓ Patients should be started on an analgesic with a strength appropriate to their assessed pain severity ✓ Mild analgesics (paracetamol, NSAIDs) should not be given alone for initiation of management of moderate or severe pain. Patients may be started on combination of paracetamol and/or NSAIDs with an opioid, such as oral morphine, if indicated by pain severity as measured on a validated numeric or visual analogue pain rating scale.
Maintenance of pain relief with opioids	*Recommendation* In adults (including older persons) and adolescents with pain related to cancer, any opioid may be considered for maintenance of pain relief (alone or in combination with NSAIDs and/or paracetamol), depending on clinical assessment and pain severity, in order to achieve sustained, effective and safe pain control. *(Strong recommendation; low quality evidence)* Remarks ✓ The correct dose of opioid is the dose that relieves the patient's pain to an acceptable level. Patient responses to opioid medicines vary by patient and vary by medicine.
	Recommendation Regularly-dosed immediate-release oral morphine, or regularly-dosed slow-release morphine, should be used to maintain effective and safe pain relief whenever oral dosing is possible. With either formulation, immediate-release oral morphine should be used as rescue medicine. *(Strong recommendation; moderate quality evidence)* Remarks ✓ Immediate-release oral morphine must be available and accessible to all patients that need it. Slow-release morphine should be made available whenever possible as an addition to, but not instead of, immediate-release oral morphine.
	Best Practice Statement When oral or transdermal routes are not possible for administration of opioids, the subcutaneous route is preferred over intramuscular injection, as this route is less painful for the patient.
Cessation of opioids	*Best Practice Statement* If a patient has developed physical dependence on opioids over the course of the management of their pain, opioid dosages should be decreased gradually to avoid withdrawal symptoms.

Adjuvant medicines for cancer pain	
Steroids	*Recommendation* In adults (including older persons) and adolescents, with pain related to cancer, adjuvant steroids may be given to achieve pain control when indicated *(Strong recommendation; moderate quality evidence)* Remarks ✓ In general, steroids should be prescribed for as short a period as possible. ✓ Optimum dosing of steroid for cancer pain depends on many clinical factors including location and type of pain, presence of or risk for infection, stage of illness, presence of diabetes mellitus, and goals of care, amongst others. ✓ When treating cancer pain or complications due at least in part to oedema surrounding a tumour, steroids with the least mineralocorticoid effect are preferable.
Management of pain related to bone metastases	
Bisphosphonates	*Recommendation* In adults (including older persons) and adolescents with bone metastases, a bisphosphonate should be used to prevent and treat bone pain. *(Strong recommendation; moderate quality evidence).*
Radiotherapy	*Recommendation* In adults (including older persons) and adolescents with pain related to bone metastases, single dose radiotherapy should be used when radiotherapy is indicated and available. *(Strong recommendation; high quality evidence)* Remarks ✓ This recommendation applies to people who already have painful bone metastases; it does not apply to people whose bone metastases are not painful.

The GDG acknowledged that other established practices exist for treatment of cancer pain but that evidence of efficacy is limited. Regarding such practices, the clinician may consider an individual trial of therapy and cease the medicine if no improvement in pain occurs. Ideally, eligible patients should be enrolled in a clinical trial wherever possible to expand the evidence base. This pertains to the following medicines and clinical regimens currently in established practice, but for which evidence of efficacy for cancer pain is lacking:

- ✓ Anti-depressants
- ✓ Anti-epileptics
- ✓ Opioid rotation

Introduction

Cancers are among the leading causes of morbidity and mortality worldwide, responsible for 8.8 million deaths in 2015. Annual cancer cases are expected to rise from 14 million in 2012 to 22 million before 2032.[1]

Pain is experienced by 55% of patients undergoing anti-cancer treatment and by 66% of patients who have advanced, metastatic, or terminal disease.[2] There are several physiological mechanisms by which cancer causes pain. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[3] Cancer and pain can also cause psychological suffering in the form of anxiety, depression, fear, or a sense of hopelessness, and anxiety and depression can in turn exacerbate pain.

The goal of pain management is to relieve pain to a level that allows for an acceptable quality of life. These guidelines focus on pain caused by the direct effect of cancer such as extension into soft tissues, visceral involvement, bone involvement, nerve compression or injury, or raised intracranial pressure, or a combination of these (Table 1). Other types of pain related to cancer can be due to side effects of treatment such as caused by nerve injury during surgery, chemotherapy-induced peripheral neuropathy, muscle spasm, lymphoedema, constipation, or pressure ulcers. These types of pain are beyond the scope of these guidelines.

Table 1: Cancer pain may be classified according to neural mechanisms:

Type			Neural Mechanism	Example
Nociceptive	Visceral		Stimulation of pain receptors on normal sensory nerve endings	Hepatic capsule stretch
	Somatic			Bone metastases
Neuropathic	Nerve compression		Stimulation of nervi nervorum	Sciatica due to vertebral metastasis with compression of L4, L5 or S1 nerve root
	Nerve injury	Peripheral	Lowered firing threshold of sensory nerves (“deafferentiation pain”)	Tumour infiltration or destruction of brachial plexus
		Central	Injury to central nervous system	Spinal cord compression by tumour
		Mixed	Peripheral and central injury	Central sensitization due to unrelieved peripheral neuropathic pain
	Sympathetically maintained		Dysfunction of sympathetic system	Chronic regional pain syndrome following fracture or other trauma

Patients with cancer may require pain relief at all stages of their disease, and not only at end of life. Better results in terms of symptom management can be achieved when palliative care is introduced early in the course of illness, through a people centred approach, concurrently with disease-modifying therapies.[4] Due to early diagnosis and improved cancer treatment, cancer patients are living longer. Nevertheless, in many settings, patients often present with cancer so advanced that any disease-modifying treatment may not be effective or feasible. For these patients, the preferred treatment option is palliative care and pain relief when needed..

The mainstay of cancer pain therapy is pharmacological interventions, but radio-therapeutic, anaesthetic, neurosurgical, psychological, physiotherapeutic, spiritual, and social interventions all play essential roles in adequate cancer pain management.

Pain relief and palliative care are an imperative of Universal Health Coverage, yet recent estimates state that 25.5 million people died in 2015 with serious health-related suffering, of which 80% lived in countries that lack access to palliative care and adequate pain relief.[5] Expert opinion and data from country experiences from several low-income countries, where treatment coverage is often low or non-existent, suggest that approximately 80% of people dying from cancer experience moderate or severe pain lasting on average 90 days.[5] Thus, cancer pain is a major cause of unnecessary suffering.

Everyone has a right to the enjoyment of the highest attainable standard of physical and mental health, and states have an obligation to take steps towards 'the creation of conditions which would assure to all medical service and medical attention in the event of sickness'.[6] This includes palliative care and access to adequate pain management. International drug control conventions state 'the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes'.[7] Palliative care and pain relief is an essential health service component of Universal Health Coverage.[8]

Despite being an issue of human rights and states' legal obligations, many people do not receive the pain relief they need. In 2011, it was estimated that 5.5 billion people (83% of the world's population) live in countries with low or non-existent access to adequate pain management.[9] Opioids are essential treatment for moderate to severe cancer pain. Even though oral morphine is on the WHO List of Essential Medicines and the list of basic essential non-communicable disease (NCD) medicines for primary health care[10], in 2015 only 43% of countries reported that it was generally available in primary care facilities in the public health sector.[11] There was a strong income gradient for this trend, with 77% of high-income countries reporting the general availability of oral morphine compared with 15% and 13% of low- and lower-middle income countries respectively.[11] Effective guidance is necessary to alleviate this preventable cancer pain pandemic.

While patients in most countries suffer from inadequate or no access to opioid analgesic medicines, an epidemic of opioid overdoses in the United States has been observed in the last two decades.[12,13] Inappropriate marketing of prescription opioids by pharmaceutical companies [14] and inappropriate prescription by medical practitioners with little attention to the development of opioid-use disorders and the risk of opioid-induced respiratory depression is postulated to have contributed to the epidemic[15].

Global treatment guidelines for cancer pain – informed by the issues outlined above - are required to ensure that active pain from cancer can be adequately managed while ensuring patient and non-patient safety. Country experiences have shown that balancing these goals is possible with appropriate measures and guidance.[16]

Former WHO cancer pain guidelines, namely *Cancer Pain Relief* (1986)[17] and *Cancer Pain Relief with a guide to opioid availability* (1996)[18], and *Cancer Pain Relief and Palliative Care in Children* (1998)[19], made seminal recommendations that set global standards for cancer pain management. Yet, there are several reasons an update is required:

The 1986 and 1996 guidelines were developed based on reports of a WHO expert committee. Current WHO guidelines are evidence-based using standardised, quality-assured methods for evidence appraisal and decision-making.

Clinical practice continues to evolve. The WHO analgesic ladder, introduced in 1986 and disseminated worldwide, remains recognized as a useful educational tool but not as a strict protocol for cancer pain treatment.[20] There are now new interventions and new delivery methods that were unavailable in 1996 (including sublingual and transdermal buprenorphine [21],[22], trans-mucosal and oral fentanyl, tramadol [23], and monoclonal antibodies), and new tools for pain assessment (Annex 1).

There is also a need to provide guidance which is suitable for the realities of low- and middle-income countries. This is especially important for instructions on the use of opioid analgesics, as accessibility and knowledge of their use remains poor in many low- and middle-income settings.

There is an ever-growing epidemiological imperative for new, up-to-date guidelines. Global cancer incidence is rising, populations are ageing, and improvement of clinical practice must meet the challenge. The provision of new guidance on cancer pain management aims to improve global clinical practice and to facilitate the removal of barriers to adequate pain relief for all who need it.

Objectives and target audience of these guidelines

The intended audience for these guidelines includes: healthcare providers, physicians, nurses, pharmacists, and caregivers, policy and programme managers, public health officials and academics. The objectives of these guidelines are:

3. To provide management guidance to healthcare providers (i.e. the end-users of these guidelines: physicians, nurses, pharmacists, and caregivers) on the adequate relief of pain associated with cancer or its treatment in adults and adolescents.

4. To assist policy-makers, programme managers, and public health personnel to create and facilitate appropriately balanced policies on opioids and prescribing regulations for effective and safe cancer pain management.

These guidelines constitute a part of WHO's efforts to promote training, improved knowledge and confidence about appropriate pain relief amongst healthcare providers and public health officials. Through their dissemination and use, it is hoped that access to effective and safe pain relief will increase, and that millions of adults and adolescents suffering from cancer pain (the people affected by this guideline) will receive the care to which they have a right. If used in the context of palliative care, guidelines for the management of cancer pain in adults and adolescents will contribute to achievement of Universal Health Coverage.

Scope of the guidelines

Pharmacological and radio-therapeutic interventions are the mainstay of cancer pain treatment. These guidelines focus on the medical management of cancer pain and make recommendations on the pharmacological and radio-therapeutic methods of cancer pain management. Anaesthetic, psychological, social, spiritual, physiotherapeutic, and surgical modes of cancer pain management are integral to comprehensive cancer pain management, and are discussed in this document, but are outside the scope of these guidelines.

These guidelines cover the management of cancer pain in adults (including older persons aged 60 or over) and adolescents (aged 10 to 19) whose cancer pain management is delivered within the health system at any level, from specialized cancer centres to primary care centres in the community and patients' homes. The recommendations apply to the full range of income settings.

Methods used in the guidelines

Full methods of the guidelines development process including the systematic review methods are provided in Annex 2.

In summary, the GDG met on 28th and 29th July 2016 to outline the scope of the guideline questions and met again on 20th and 21st November 2017 to deliberate and determine the recommendations made in response to 13 key clinical questions. The questions included optimal choice of medicines for initiating and maintaining cancer pain relief, managing breakthrough pain, use of adjuvant medicines including steroids, anti-convulsants, and anti-epileptics, for cancer pain relief, and optimal management of bone pain. See Annex 4 for the full details of the clinical questions.

Systematic reviews for each questions were completed by independent review teams in advance of the meeting and shared with the GDG prior to the meeting. This included a network meta-analysis comparing different groups and classes of analgesic medicines for managing cancer pain.

Outcomes were rated by GDG members according to the importance of each outcome from the perspective of the person living with cancer pain as 'not important' (1 – 3), 'important' (4 – 6), or 'critical' (7 – 9). Those outcomes rated as critical were included in final GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence Profile Tables which were presented to the GDG for determining the balance between benefits and potential harms. The steps undertaken for the retrieval of evidence, assessment, and synthesis are summarized in Annex 2.

For making recommendations on interventions, GRADE methodology as defined in the WHO guidelines handbook was used to provide a rating of the overall quality of evidence arising from each systematic review and categorised as very low, low, moderate or high.

Values and preferences of the intervention were considered from the perspectives of patients. These perspectives were offered and discussed by the GDG members, all of whom had broad professional experience and observations of the field. A GDG member from Human Rights Watch presented patient experiences for each question under discussion.

When considering resources use, the GDG were presented with pricing of drugs where these were available and brought their knowledge of medication prices from around the world to the considerations. No formal cost-effectiveness studies were conducted, but the GDG considered the longer-term benefits of each recommendation in terms of possible reductions in hospitalisation and morbidity.

The GDG proffered observations and their own experiences regarding the acceptability of interventions to healthcare workers and the feasibility of implementation of recommended interventions, especially in regions were resources are scarce or absent. Similarly, the effect of provision of an intervention on equity was carefully considered through discussion within the GDG. No formal patient or healthcare provider surveys were conducted.

Based on the agreed quality of the evidence and with consideration given to the values and preferences of patients, the acceptability and feasibility of the intervention within the healthcare system, the potential impact on equity, and the resource implications, the GDG decided on the direction of the recommendation (either in favour or against an intervention) and whether to make

strong or *conditional* recommendations using a benefit/risk assessment analysis of each intervention. In the absence of any evidence for a certain review question, the GDG chose to make no recommendation.

For several questions where evidence was scant or lacking, the GDG recognised that established practices exist but did not formulate recommendations for or against the practices. For two such questions, best practice statements were formulated instead given the potential benefit and lack of any observed harms from current practices. For those questions where harms or lack of effect was less certain specifically in patients with cancer pain, the GDG advocated that clinicians conduct an individual trial of therapy in their patients and assess the response accordingly. Ideally, and wherever possible, clinicians are encouraged to enrol eligible patients into a clinical trial to establish efficacy and build the evidence base.

Conflicts of interest were managed by requesting all GDG members to complete a WHO Conflicts of Interest (COI) form in advance of the meeting and declare these before the entire GDG. Relevant declared interests of GDG members are reported in Annex 4. None of the declared interested were considered by the WHO secretariat to be conflictual. WHO policies on COI were fully applied throughout.

Cancer Pain Management – Guiding Principles

The group of experts and stakeholders that developed the guidelines, the GDG, determined that all recommendations arising from the meeting would be underpinned by the following over-arching principles of effective health systems and best clinical practice:

1. *The goal of optimum management of pain is to reduce pain to levels which allow an acceptable quality of life.*

While as much as possible should be done clinically to relieve a patient's pain from cancer, it may not be possible to eliminate pain completely in all patients. The goal of pain management, therefore, is to reduce pain to a level that allows for a quality of life that is acceptable to the patient. The benefit of pain relief must be balanced against the risk of adverse effects and overdose that may result in respiratory depression.

A diagnosis of 'refractory pain' should not be made too early as apparently 'refractory pain' may simply be due to a lack of access to state-of-the-art pain treatment. Invasive interventions for pain, such as nerve blocks, may be unnecessary when pain management guidelines are followed.

2. *Global assessment of the person should guide treatment, recognizing that individuals experience and express pain differently.*

The first step in cancer pain management should always be assessment of the patient. The assessment should be as comprehensive as possible consistent with the patient's comfort and should include a detailed history, physical examination, assessment of psychological circumstances, an assessment of pain severity using an appropriate pain measurement tool, and indicated diagnostic procedures. Early identification of patients with potential cancer pain should be performed proactively in all care settings, and especially in primary care.[24] Assessment and re-assessment at regular intervals are key to ensuring treatment is appropriate and safe, as well as minimizing and addressing side-effects over the course of a patient's care plan.[25]

Annex 1 provides examples of pain assessment scales for specific populations.

3. *Administration of analgesic medicine should be given "by mouth", "by the clock", "for the individual", and with "attention to detail":*

By mouth:

Whenever possible, analgesics should be given by mouth.

By the clock:

Doses of analgesic should be given at the appropriate fixed intervals of time. The dose should be gradually increased until the patient is comfortable. The next dose should be given before the effect of the previous dose has worn off.

For the individual:

Management of an individual patient's pain requires careful assessment as described in item 2 above, differential diagnosis of the type of pain (for example, nociceptive somatic pain or nociceptive visceral

pain or neuropathic pain), the site of origin of the pain, and then a decision about optimum treatment. The correct dose is the dose that relieves the patient's pain to a level acceptable to the patient.

Previous WHO guidance included a pain management ladder which has been widely used in the cancer care community (See http://www.who.int/cancer/palliative/painladder/en/). However, a pain management ladder is only a general guide to pain management (See Annex 1). With respect to opioids, patient responses may vary by patient and by medicine. At times, adverse effects or patient choice may preclude escalation. It is therefore useful if multiple opioid medicines are accessible, since each has slightly different properties. It is essential that oral immediate-release and injectable morphine be accessible everywhere.

With attention to detail:

The first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally, the patient's analgesic medicine regimen should be written out in full for the patient and their family to work from, including the names of the medicines, reasons for use, dosage, and dosing intervals. Patients should be warned about possible adverse effects of each of the medicines they are being given.

4. Analgesics, including opioids, must be accessible: both available and affordable

Opioid analgesics are essential for the adequate treatment of moderate and severe cancer pain. Yet access and availability are poor in most low- and middle-income countries. Barriers to adequate pain relief include: regulatory and legal barriers, attitude and knowledge barriers, and economic and procurement impediments.[26] Addressing all of these barriers will be necessary in a country to increase access to adequate pain relief. In many settings, cancer pain management will be impossible unless policy changes enable access to adequate pain relief medicines. These issues are comprehensively addressed in *Ensuring balance in national policies on controlled substances (2011).*[27] Clinical and policy guidelines should be complementary in order to increase overall access to controlled pain relief medicines. Annex 5 presents International Conventions on availability of opioid analgesics.

5. A pain management plan includes pharmacological treatments, and may include psychosocial and spiritual care.

Pain is an outcome of a person's biological, psychological, social, cultural, and spiritual circumstance. Therefore, while **pharmacological interventions are the mainstay of cancer pain management,** psychosocial care is also an essential component of a comprehensive care plan. Healthcare teams should include this aspect of care when devising patient care plans, enabling supportive and culturally appropriate counselling for patients and their families. Care plans should allow for spiritual counselling appropriate to the beliefs of the patient and family. Cancer patients may experience depression, fear, and anxiety. A very anxious or depressed patient should receive appropriate therapy, which may be pharmacological or otherwise, for their psychological needs in addition to an analgesic. If the psychological as well as physiological aspects of pain are not treated, the pain may remain intractable.

6. *Safety of patient, carer, healthcare provider, community and society*

Provision of analgesia for cancer pain management can carry risks to the safety of patients, their family, and society more broadly. Therefore, proper and effective stewardship of opioid analgesics in the cancer treatment setting is essential to ensure the safety of patients and to reduce the risk of medicine diversion into society. The safety of healthcare providers may also be at risk if providers are coerced into diversionary activities, threatened for access to medicines, or at risk of abuse themselves.

Patient assessment should pay close attention to patients' psychological history, their patterns of opioid consumption, and any history of substance use, to identify risk factors for improper use and signs of substance use disorders that should influence clinical decision-making.

The presence of opioids in households presents a risk of misuse or unintentional overdose by children, adolescents, and other household members. Safe, secure storage of opioid analgesics should be optimised at a household level and provision made for the safe disposal or return of unused opioid medicines to a pharmacy at the end of life or when no longer needed.

7. *Cancer pain management should be integrated as part of cancer care*

Cancer pain management should be integrated into cancer treatment plans throughout the care continuum, including when a patient's disease is not terminal, as necessary. Treatment should begin by giving the patient an understandable explanation of the causes of their pain. Anti-cancer treatment and pharmacotherapy for cancer pain relief should be given concurrently if the patient is in pain.

Recommendations for the pharmacologic and radio-therapeutic management of cancer pain in adults and adolescents.

The following pages present the recommendations and underlying rationale of the expert Guidelines Development Group.

For ease of reference, the recommendations included in these guidelines refer to classes of medicines outlined in Table 2.

Table 3 presents the cost of some essential pain medicines in countries of different income levels, and Annex 6 contains the pharmacological principles of cancer pain management.

Table 2: Groups and classes of medicines for cancer pain management and specific examples

Medicine Group	**Medicine Class**	**Example Medicines**
Non-opioids	Paracetamol	Paracetamol oral tablets and liquid. Rectal suppositories, injectable
	NSAID	Ibuprofen oral tablets and liquid Ketorolac oral tablets and injectable Acetylsalicylic acid oral tablets and rectal suppositories
	Metamizole	Metamizole oral tablet and injectable
Opioids	Weak opioids	Tramadol oral tablet and injectable Codeine oral tablets and liquid and injectable
	Strong opioids	Morphine oral tablet and liquid and injectable Hydromorphone oral tablets and liquid and injectable Oxycodone oral tablets and liquid Fentanyl injectable, transdermal patch, trans-mucosal lozenge Methadone oral tablet, liquid, injectable
Adjuvants	Steroids	Dexamethasone oral tablet and injectable Methylprednisolone oral tablets and injectable Prednisolone oral tablets
	Anti-depressants	Amitriptyline oral tablets Venlafaxine oral tablets
	Anti-convulsants	Carbamazepine oral tablets and injectable, Gabapentin oral tablets
	Bisphosphonates	Zoledronate injectable Pamidronate injectable
Others	Cannabinoid	Nabiximols oral spray
	Monoclonal antibody	Denosumab injectable
	Naloxone	Naloxone injectable

Table 3: Cost to hospitals in 2015 of selected essential medicines for pain management in US dollars in countries of various income levels

Medicine	Low-income country (Rwanda)	Low-middle-income country (Vietnam)	High-middle-income country (Mexico)
Morphine 10mg immediate-release oral	0.13	0.09	0.11
Morphine injectable 10mg ampule	1.17	0.13	7.73
Dexamethasone injectable 4mg ampule	0.13	0.04	0.27
Amitriptyline 25mg tablet	0.01	0.01	0.03
Paracetamol 500mg tablet	0.01	0.02	>0.01

Source: Knaul FM, Farmer PE, Krakauer EL, et al. on behalf of the Lancet Commission on Palliative Care and Pain Relief Study Group. Alleviating the access abyss in palliative care and pain relief: an imperative of universal health coverage. Lancet 2018; 391: 1391-1454.

1. Initiation of pain relief

In this section we present the recommendation, supporting evidence and rationale for the key clinical question to determine the optimal medicines to use when initiating analgesia in patients with cancer pain (see Annex 4 for details of the questions). During the scoping meeting the GDG determined that there was uncertainty whether initiation of analgesia should include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, or opioids, either alone or in combination. The intention was to conduct a network meta-analysis to allow for direct and indirect comparisons, but too few trials were eligible and an NMA was not possible.

Recommendation

In adults (including older persons) and adolescents with pain related to cancer, NSAIDs, paracetamol, and opioids generally should be used at the stage of initiation of pain management, either alone or in combination, depending on clinical assessment and pain severity in order to achieve rapid, effective and safe pain control. *(Strong recommendation; low quality evidence)*

Remarks

- ✓ Patients should be started on a type and strength of analgesic appropriate to their type and severity of pain.
- ✓ Mild analgesics (paracetamol, NSAIDs) should not be given alone for initiation of management of moderate or severe pain. Patients may be started on a combination of paracetamol and/or NSAIDs with an opioid, such as oral morphine, if indicated by pain severity as measured on a validated numeric or visual analogue pain rating scale.

Considerations

Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), morphine, and other opioids have been regarded as mainstays of cancer pain treatment for decades and remain so today [28-30]. Paracetamol, ibuprofen, and several opioids are included in the WHO Model List of Essential Medicines for Pain and Palliative Care. Since there is known clinical variation in patients' response to specific analgesic medicines, ideally a range of opioid analgesics should be accessible to adult, adolescent, and older patients with cancer pain.

Co-formulations of combined opioid and non-opioid analgesics are discouraged because of the loss of ability to titrate each analgesic independently, and the risk of exposure to high, potentially toxic doses of the non-opioid analgesics such as paracetamol or ibuprofen.

Summary of the evidence

Evidence was derived from pair-wise comparisons from five trials although none clearly distinguished between patients at pain management initiation and those on maintenance treatment. Inclusion was based on the fact that all five trials included people with cancer pain who were naïve to strong opioids (or were beginning opioid treatment). The studies evaluated buprenorphine, fentanyl, morphine, oxycodone, with a single trial comparing weak opioid + NSAID to NSAIDs.

Two of the five trials compared medicine classes to evaluate relief of pain, providing very low strength of evidence favouring strong opioids to relieve pain more frequently than weak opioids (RR 1.80; 95% CI 1.42, 2.29) and favouring combination weak opioids + NSAID to relieve pain more frequently than NSAIDs alone (RR 1.36; 95% CI 0.98, 1.87).[31,32] One of the trials also evaluated degree of pain relief, providing very low strength of evidence regarding strong opioids compared with weak opioids,

suggesting no difference (estimated net difference = -3.3; 95% CI -87, 60 on a scale of 0 to 100 [worst]).[31]

Three eligible RCTs evaluated outcomes other than pain relief among people with cancer who were initiating pain management.[33-35] These three trials together provided moderate strength of evidence of similar rates of confusion with either morphine or oxycodone (RR = 0.85; 95% CI 0.50, 1.44), nominally favouring morphine. One trial compared all four opioids, providing low strength of evidence of similar rates of confusion with all four medicines (from 36% to 47%).[35] No studies reported on quality of life specifically. No trial listed or reported on respiratory depression among their study participants.

Rationale

The RCT evidence on the selection of a particular type of analgesic over others for pain relief was of low quality, but the GDG noted that this uncertainty was related to selection of analgesic and not uncertainty about whether to use analgesics or not to obtain pain relief. Moderate quality evidence for adverse effects indicated that there was little difference between analgesics. The GDG observed that although patients valued the pain relief delivered by analgesia, patients may have concerns regarding initiating opioids in particular and that values and preference related to type of analgesia were likely to vary across countries, cultures, clinicians, families, and patients. With respect to opioid administration, the GDG noted that acceptability to healthcare workers and feasibility of provision were likely to be highly variable regionally, although there was agreement that healthcare workers aimed to relieve the pain experienced by their patients and would value greater analgesic options. The GDG also bore in mind the risk of unintended consequences. They noted that balanced regulations on strong opioid medicines, which balance the necessity of their availability to patients who need them with the necessity of tackling their misuse, are possible. Recommendations on how to achieve this balance are presented in other WHO documents.[27]

The GDG observed that a recommendation to provide greater access to analgesia at initiation of pain management may be resource-intensive and changes may be required to the regulatory environment in some countries to facilitate this. However, given that the majority of the global population currently does not have access to adequate analgesia, with this inequity likely to increase with the expanding burden of cancer in low- and middle-income countries, the GDG determined to make a strong recommendation in favour of provision of a selection of analgesics for pain management initiation despite the low quality evidence.

2. Maintenance of pain relief

In this section we present the recommendations, supporting evidence and rationale for each of five key clinical questions related to maintaining pain relief following initiating effective relief of pain in patients with cancer pain.

The questions were 1) which is the most effective opioid for maintaining pain relief, 2) which is the most effective opioid for treating breakthrough pain, 3) what is the evidence for the practice of opioid rotation or opioid switching as compared with continuing use of one opioid, 4) what is the evidence for the benefit of administering modified release morphine regularly as compared with immediate release morphine on a 4-hourly or on an 'as required' basis, and 5) is there benefit for using the subcutaneous, transdermal, or transmucosal routes as compared with the intramuscular and intravenous routes when the oral route for opioids is inappropriate (see Annex 4 for list of detailed questions).

2.1. Choice of opioid

Recommendation

In adults (including older persons) and adolescents with pain related to cancer, any opioid may be considered for maintenance of pain relief, depending on clinical assessment and pain severity, in order to sustain effective and safe pain control. *(Strong recommendation; low quality evidence)*

Remarks

- ✓ The correct dose of opioid is the dose that relieves the patient's pain to an acceptable level. Patient responses to opioid medicines vary by patient and vary by medicine.

Considerations

The choice of analgesic medicine, dosage, and timing should be guided by the specific pharmacokinetics of each opioid medicine, their contraindications, and their adverse effects in different patients; the dose or medicine that successfully relieves pain for one patient will not necessarily do so for others. Therefore, while it is imperative that oral immediate-release and injectable morphine are accessible to everyone, it may be optimal if a range of opioid medicines is accessible to patients, since the medicine that is most appropriate for one patient will not necessarily be appropriate for another.

Summary of the evidence

Thirty-eight eligible RCTs evaluated outcomes of interest among people with cancer who were being managed for their cancer pain.[36-73] However, few trials clearly distinguished between patients at pain management initiation and those on maintenance treatment, and classification was dependent on the reviewers' judgement.

Direct and indirect evidence from 13 trials included in the Network Meta-analysis (NMA) provided high quality evidence that a combination of strong opioid and NSAID reduces pain (measured on a continuous scale) better than alternative analgesics (See Annex 7 Network Meta-analysis League Table 1 and League Table 2).[51,52,61,74,65-73] Direct and indirect evidence from six trials reporting on pain relief as a dichotomous response provided low quality evidence that there may be no differences between analgesics for relief of pain [41,63,64,70,75,76].

Direct evidence for outcomes other than pain relief was obtained from 26 trials comparing different analgesic treatments.[36-49,51-62] The trials evaluated 14 classes of analgesics with 12 studies conducted in older persons.

Direct evidence from five trials evaluated duration of maintenance of pain reduction. There is low strength of evidence of no significant differences among the interventions (codeine, codeine + ibuprofen, diclofenac, morphine ER (every 12 hours), ketorolac, morphine CR, and morphine IR). Four trials evaluated speed of pain relief, providing low strength of evidence of no significant difference among codeine, codeine + ibuprofen, diclofenac, ketorolac, morphine slow-release, morphine immediate-release, and oxycodone slow-release. The studies evaluated different outcomes, which ranged from minutes to days.

One trial found no significant difference in quality of life, as measured by the EORTC QTQ-C30, between celecoxib and placebo (very low strength of evidence). There was a difference of 2 on a scale of 0 to 100 [best], but no further data were reported.

Seventeen trials reported on sedation, using various definitions within studies including sedation, somnolence, drowsiness, and tiredness. The rates of sedation were heterogeneous across ten interventions with pooling of two trials providing low quality evidence of no difference in the risk of sedation between fentanyl and morphine slow-release yielding a RR of 0.88 (95% CI 0.52, 1.48). One of the trials explicitly discussed respiratory depression (in fact “respiratory failure”) as an adverse event, with a single occurrence reported among 62 people taking tapentadol, but none with morphine slow-release. The studies did not report data to allow evaluation of subgroup differences.

Overall, the evidence indicates that a combination of high potency opioid combined with an NSAID is better than alternative analgesics for maintenance of pain relief, with no evidence of inconsistency in the data. However, the choice of opioid analgesic may make little or no difference in speed of pain relief, duration of maintenance of pain reduction, or functional outcomes.

Rationale

The evidence does not indicate that there is an obviously-best opioid for maintenance of pain relief. The systematic review reveals some differences between the medicines with regards to adverse effects, which may influence patient and clinical preference. The GDG acknowledged that many differences between opioid medicines are often overstated. The GDG believed that there was minor variability in the patient values and preferences for one opioid over another although individual responses to adverse effects may influence patient choice. The GDG agreed that provision of all analgesic options were likely to be acceptable to key stakeholders such as clinicians and policy-makers, but recognised that, as for choice of initiation analgesia, there is likely to be variability in the acceptability of opioids in many settings worldwide. The GDG also bore in mind the risk of unintended consequences with diversion a concern. However, they noted that balanced regulations of these strong analgesics, which balance the necessity of their availability to patients who need them for pain management with the necessity of tackling their misuse, are possible. Recommendations on how to achieve this balance are presented in other WHO documents.[27]

The GDG recognised that while increasing the availability of opioids would require an increase in resources including additional training for healthcare workers, they argued that good pain control leads to an improvement in patient functional status and that appropriate palliative care may be cost-effective. The cost of medicines would be an important factor in decisions to make certain medicines

available. In low-resource settings, cheaper medicines are preferred as the clinical differences between those and the more expensive medicines are small. Provision of opioids should also improve equity globally with regard to these medicines. For these reasons, the GDG determined that the recommendation would be strong.

2.2. Treatment of breakthrough pain

Breakthrough pain in cancer refers to a transitory flare of pain in the setting of chronic pain managed with pain medicines around the clock.[77]

Best Practice Statement

Breakthrough pain should be treated with a rescue medicine, which should be an opioid such as morphine in its immediate-release formulation.

Considerations

The regularity of administration should be appropriate to the medicine. In addition to regular administration, patients should have access to a rescue medicine. A rescue dose that is 50-100% of the regular four hourly dose may be considered. In the absence of evidence, the choice of specific medicine may depend on affordability and ease of administration. As per recommendation 3, it should be an immediate-release opioid, not a slow-release opioid.

Summary of the evidence

A single small RCT (N = 68) compared analgesics specifically for management of breakthrough pain in an older population with multiple cancer types.[42] The trial provided low strength of evidence that the choice between sustained-release and immediate-release morphine may make no difference to prevent breakthrough pain (OR 1.00; 95% CI 0.75, 1.33) or to reduce pain (summary difference on a 0 to 100 [best] scale = -0.2; 95% CI -1.0, 0.6). The trial did not report on pain relief speed, pain relief maintenance, quality of life, functional outcomes, or respiratory depression. The trial provided very low strength of evidence, regarding differences between sustained-release and immediate-release morphine to avoid confusion. In the cross-over study, two patients developed confusion while taking immediate-release morphine, but the confusion was not attributed to the opioids.

Rationale

The GDG agreed that they could not justify making a recommendation on the basis of only one eligible low quality RCT that looked at too few of the options available clinically. The GDG also noted a high degree of uncertainty regarding patient values and preferences, acceptability and feasibility. However, the GDG wished to highlight that the cost of certain formulations, such as transmucosal fentanyl, was likely to be prohibitively expensive for some low- and middle-income settings, and cheaper medicines such as immediate-release oral morphine, should be made available as a priority if they are not already available. Given the urgent need for guidance to manage breakthrough pain for both patients and clinicians, the GDG selected to make a best practice statement that breakthrough pain should always be relieved with rescue medicine based on clinical experience and patient need.

This best practice statement was congruent with the recommendation on choice of immediate- or slow-release morphine (See Section 4.4.) and was therefore incorporated into the recommendation and therefore does not appear as a stand-alone Best Practice Statement.

2.3 Switching or rotating opioid medicines

Patients receiving increasing doses of an opioid for inadequately controlled cancer pain may develop adverse effects before achieving an acceptable level of analgesia. It has been proposed that opioid switching might improve the balance between analgesia and adverse effects.[78,79]

No Recommendation

In the absence of evidence, WHO makes **no recommendation for or against** the practice of opioid switching or rotation.

Considerations

In the absence of any evidence, practitioners may wish to consider an individual trial of therapy and to switch to another opioid for those patients who do not achieve adequate analgesia or have side-effects that are severe, unmanageable, or both.

Ideally clinicians should identify active clinical trials testing the efficacy of opioid rotation in patients with cancer pain and, wherever possible, encourage eligible patients to enrol into such trials.

Summary of the Evidence

No RCTs were identified that evaluated switching or rotating opioids in patients with cancer pain.

2.4. Choosing between immediate-release morphine and slow-release morphine

Recommendation

Regularly-dosed immediate-release oral morphine, or regularly-dosed slow-release morphine should be used to maintain effective and safe pain relief. With either formulation, immediate-release oral morphine should be used as rescue medicine. *(Strong recommendation; moderate quality evidence)*

Remarks

- ✓ Immediate-release oral morphine must be available and accessible to all patients that need it. The availability of slow-release morphine is optional as an addition to, but not instead of, the availability of immediate-release oral morphine.

Considerations

Patients sometimes place high value on the availability of both formulations, therefore both options being available is preferred, if resources allow. If a health system must choose between one or the other formulation, immediate-release oral morphine should be chosen as it can be used as both maintenance and rescue medicine whereas slow-release morphine cannot be used for rescue.

Summary of the evidence

Ten eligible RCTs compared modified-release morphine (morphine SR) versus immediate-release morphine.[37,42,49,80-87] Participants had a variety of cancer types in almost all trials. Study participants generally had moderate or severe pain (or the level of pain severity was not explicitly described). The trials evaluated a variety of formulations of morphine slow-release (MS Contin®, Oramorph SR®, Skenan®, MST Continus®, Kapanol®, or defined formulations). One trial used ketobemidone for breakthrough pain; the others used morphine immediate-release. All studies (at least implicitly) prescribed the morphine immediate-release to be taken on a fixed schedule.

There is moderate strength of evidence of no difference in pain relief between slow- and immediate-release morphine. Meta-analysis of four trials (N = 222) which reported on pain relief as a categorical outcome yielded a summary RR = 0.99 (95% CI 0.95, 1.03). A meta-analysis of four other trials found similar pain scores among participants measured on a continuous scale (SMD: transformed to a 0 to 100 [worst]) scale) was -0.6 (95% CI -5.9, 4.8).

One small trial provided low strength of evidence of no difference in pain relief speed (time to achieving stable pain control, difference between arms -0.4 days; 95% CI -1.1, 0.3). The same trial provided very low strength of evidence of no difference for quality of life, with a difference between arms of 9 points (on a transformed scale of 1 to 100 [best]) with 95% CI -6 to 24). No eligible studies evaluated pain reduction maintenance or functional outcomes. Two studies provided low quality evidence of no difference between immediate- and slow-release morphine in sedation scores. Only two trials explicitly reported on respiratory depression as a potential adverse event. They provided low strength of evidence finding no events in a small overall sample of patients (n = 126). None of the RCTs evaluated subgroups of interest.

Rationale

The choice of slow-release and immediate-release morphine probably makes little or no difference to pain relief and may make no difference to pain relief speed, maintenance of pain relief, and sedation. Respiratory distress events may be rare with both formulations. The GDG agreed that there was no clear benefit of one formulation over another. The GDG observed that some patients may prefer slow-release morphine because of the lower pill burden, more sustained analgesia, and less waking at night and that there was likely to be major variability among patients with regard to choice of formulation. In other patients there may be stigma against certain formulations. Slow-release morphine is typically more expensive than immediate-release morphine. It was not clear which formulation was more cost-effective and the GDG noted that the variability in resource requirements was likely to be minor. The GDG remarked that today in many countries, patients might only have access to slow-release morphine and that this is inadequate to maintain treatment of breakthrough pain. In other settings, patients may have access to immediate-release morphine, but only in the injectable form which is not appropriate to the outpatient setting. Given that provision of both formulations was highly likely to be acceptable to healthcare workers and feasible to implement, the GDG made a strong recommendation with the proviso that the priority medicine is immediate-release oral morphine, with other formulations as acceptable *additional* options.

2.5. Route of administration of opioids

Oral administration of opioids usually is preferable whenever possible to avoid the discomfort, inconvenience and expense of parenteral administration. However cancer patients often become unable to take oral medicines at some point in the course of their illness due, for example, to dysphagia, bowel obstruction, or vomiting.[18] Therefore, other routes of opioid administration are often needed.

Best Practice Statement

When oral or transdermal routes are not possible, the subcutaneous route is preferred over intramuscular injection, as this route is less painful for the patient.

Summary of the evidence

A single small cross-over trial compared non-invasive routes versus injected routes for opioids in 20 adults with multiple types of cancer who were selected for the trial due to substantial side effects related to oral or rectal opioids.[88] There was very low strength of evidence suggesting no difference in degree of pain relief between subcutaneous and intravenous hydromorphone (difference = 3.0; 95% CI -15, 21) on a 0 to 100 (worst) scale). The trial did not report on critical or important adverse events The trial found that sedation, measured by visual analogue scale, improved in both arms with opioid treatment.

Rationale

The GDG could not make a new recommendation on the basis of the very low quality and limited amount of evidence. However, there was consensus that oral or transdermal routes are preferred. When it is possible to administer medicines via either of the oral or transdermal routes, the GDG agreed that the subcutaneous route is preferred over intramuscular injection, as this route is less painful for the patient. A Best Practice Statement was thus formulated.

3. Cessation of opioid use

If the cause of cancer pain is effectively addressed by anti-cancer treatment (for example, surgery or chemotherapy), it follows that the use of opioids is no longer necessary and an opportunity exists to decrease or stop opioid use. The GDG developed a clinical question regarding the optimal tapering regimens of interventions to effectively and safely cease use of opioids specifically in patients who have received opioids for cancer pain (see Annex 4 for detailed question).

Best Practice Statement

If a patient has developed physical dependence on opioids over the course of the management of their pain, opioid dosages should be decreased gradually to avoid withdrawal symptoms.

Summary of the evidence

No eligible studies were found that address this question.

Rationale

The GDG could not make a new recommendation in the absence of evidence. The GDG selected to provide a table outlining a general guide to opioid cessation (see Annex 6) and to make a Best Practice Statement regarding opioid cessation when a patient has developed physical dependence on opioids.

After an abrupt reduction in pain (such as after a nerve block or neuro-ablative procedure), clinicians may consider reducing the dose of opioid until it can be stopped. Following radiotherapy or other anti-cancer treatments, pain relief may be much slower and take days to weeks. If the pain-relieving procedure has been successful, clinicians may consider slowly reducing the dose of opioid, titrated against the patient's response, until it can be stopped completely if the pain does not recur. Close and regular assessment is needed. If pain recurs, clinicians should take care to suspend dose reduction temporarily and/or to increase the dosage again if necessary until adequate pain relief is achieved.

Efficacy data are available from clinical trials of opioid cessation in people with opioid dependence undergoing managed withdrawal [89,90]. However, it is not clear if patients with cancer pain will respond to the evidence-based regimens similarly to individuals without cancer and whether optional substitution therapy is desirable in this group of patients. This uncertainty notwithstanding, practitioners looking after patients with cancer may wish to consult and liaise with a specialist in substance use disorders to develop and implement an individualised opioid cessation plan for patients who no longer require opioid analgesia.

4. Adjuvant medicines for cancer pain management

Adjuvant analgesics used in conjunction with opioids have been found to be beneficial in the management of many cancer pain syndromes; however, they are currently underutilized. Adjuvant drugs may be necessary to enhance pain relief such as corticosteroids in nerve compression or to treat concomitant psychological disturbances such as insomnia, anxiety and depression (sedatives and antidepressants) [17].

4.1. Steroids

Steroids are among the most commonly used as adjuvant medicines for management of cancer pain of several types: metastatic bone pain, neuropathic pain, and visceral pain.[84,91]

Recommendation

In adults (including older persons) and adolescents, with pain related to cancer, adjuvant steroids should be given to achieve pain control when indicated *(Strong recommendation; moderate quality evidence)*

Remarks

4. In general, steroids should be prescribed for as short a period as possible.
5. Optimum dosing of steroid for cancer pain depends on many clinical factors including location and type of pain, presence of or risk for infection, stage of illness, presence of diabetes mellitus, and goals of care amongst others.
6. When treating cancer pain or complications due at least in part to oedema surrounding a tumour, steroids with the least mineralocorticoid effect are preferable.

Considerations

Appropriate doses of steroids differ depending on the indication and medicine. Following an initiation dose, the dose should be reduced over time and the optimal maintenance dose should be determined by the analgesic requirement of the patient.

Care should be taken with regard to patient selection for the prescription of steroids because some patients may have contraindications.

Summary of the evidence

Seven eligible trials compared steroids to placebo (see Annex 3, Evidence Profile 5.1) in patients with a variety of cancers.[92-98] The studies evaluated methylprednisolone (4 trials), dexamethasone (2 trials), and prednisolone (1 trial).

Five trials provided moderate strength of evidence that pain relief was greater in patients taking steroids than placebo. The summary net difference in pain scores between arms was -9.9 (on a 0 to 100 [worst] scale), 95% CI -16.0 to -3.8, favouring steroids. Over half the weight for this summary estimate came from the only trial that found a statistically significant finding, which also reported the greatest reduction in pain scores with steroids, and was published in 1985.

None of the trials reported pain relief speed or duration of pain relief maintenance. Three studies provided very low strength of evidence that patients taking steroids had improved quality of life compared with placebo with a summary net difference (on a 0 to 100 [best] scale) of 12.6 (95% CI 6.2, 19.0). One small trial provided very low strength of evidence regarding gastrointestinal bleeds, being the only study to explicitly report this adverse event. No gastrointestinal bleeds occurred among 31

patients in this crossover study. Two small studies reported on psychiatric adverse events: one trial provided very low strength of evidence regarding depression, with very imprecise estimates of no difference (RR = 1.00; 95% CI 0.06, 15.2); the other trial provided very low strength of evidence regarding both anxiety and "psychic change" (undefined) in favour of steroids (both RR = 0.59; 95% CI 0.11, 3.20). No study reported on delirium or psychosis.

There were no trials that compared the effects of different steroids against other steroids.

Rationale

Moderate quality evidence indicates that steroids probably improve pain relief and may improve quality of life, but it is uncertain whether in this population steroids increase risks of gastrointestinal bleeds or psychiatric adverse events. The GDG remarked that patients, especially young patients, are sometimes reluctant to take the medicines due to their known common side-effects. Older patients are also sometimes reluctant on account of diabetes and other comorbidities. The GDG deemed the option acceptable to clinicians, who frequently appreciate the speed of onset of steroids' beneficial effects. The resource requirements are small, and the option is feasible. The GDG did not believe the therapy would have much impact on equity. The GDG noted that while some side effect and adverse events from steroids can be serious, the balance of effects is in favour of their use when indicated and made a strong recommenation. However, the GDG observed that the absence of evidence comparing different steroids did not support a recommendation in favour of any single specific steroid over another.

4.2. Anti-depressants

Cancer-related neuropathic pain is common and can be caused either by the disease or by cancer treatment. Two classes of anti-depressants, tricyclic anti-depressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs), are commonly used as adjuvants medicines to treat neuropathic pain.

No Recommendation

WHO makes **no recommendation for or against** the use of anti-depressants to treat cancer-related neuropathic pain.

Considerations

In the absence of high quality evidence specific to treating tumour-related neuropathic pain, the GDG noted the efficacy data from anti-depressant use in non-cancer neuropathic syndromes and suggested that practitioners may wish to consider an individual trial of therapy with an anti-depressant for patients with cancer-related neuropathic pain that is not relieved adequately by a combination of an opioid and either paracetamol or NSAIDs, or both. Care should be taken to evaluate the effectiveness after adequate titration and treatment should be stopped if not beneficial. Ideally eligible patients should be enrolled in a clinical trial to establish efficacy in cancer pain and practitioners are encouraged to seek out such trials and facilitate enrolment of eligible patients.

Summary of the evidence

One eligible trial compared amitriptyline to placebo in 60 people with severe neuropathic cancer pain (cancer types and ages not reported).[99] There was low quality evidence that amitriptyline is more effective than placebo to reduce pain in people with cancer-related neuropathic pain; the net difference in VAS score (transformed 0 to 100 [worst] scale) was -4.7 (95% CI -9.2, -0.2). The trial did not report data on complete pain relief, pain relief speed, pain reduction maintenance, quality of life, functional outcomes, or adverse events.

No eligible trials were found that compared different anti-depressants to others.

Rationale

While decades of clinical practice have shown anti-depressants to be effective in neuropathic pain syndromes[100], the GDG did not feel sufficiently confident that the evidence indicates their effectiveness in tumour-related neuropathic pain . They therefore opted to make no recommendation due to lack of evidence. They also noted that some patients might have strong aversions to the use of anti-depressants due to stigma and that possible anticholinergic side-effects, such as dry mouth, constipation or sedation, may be an additional burden.

There were no eligible trials found that compared different anti-depressants with each other. The GDG could not make a recommendation for one anti-depressant over others due to absence of evidence.

4.3. Anti-convulsants

Cancer-related neuropathic pain is common and can be caused either by the disease or by cancer treatment. Anti-convulsants are commonly used as adjuvants medicines to treat neuropathic pain. Certain anti-epileptics have been reported to be effective for treatment of neuropathic pain (See Fallon 2013[100] for review), including gabapentin, pregabalin, carbamazepine and valproate

Recommendation

WHO makes **no recommendation for or against** the use of anti-epileptics/anti-convulsants for the treatment of cancer-related neuropathic pain.

Considerations

In the absence of clear evidence in favour of anti-epileptic, the GDG suggested that practitioners may wish to consider an individual trial of therapy and prescribe an anti-epileptic for those patients who do not achieve adequate analgesia or have side-effects that are severe, unmanageable, or both.

Ideally clinicians should identify active clinical trials testing the efficacy of anti-convulsants in patients with cancer pain and, wherever possible, encourage eligible patients to enrol into such trials.

Summary of the evidence

The results of the systematic review were not presented. The evidence retrieved for the systematic review for this question was discounted due to a revelation of fraud. While gabapentin has been widely prescribed, in 2017 it was rejected for inclusion in the WHO Essential Medicines List on account of fraudulent evidence.[101-104]

Rationale

The fraudulent data called into question the systematic review data for this question, resulting in no recommendation being made. The fraudulent data is specific to gabapentin but the review analyses included gabapentin and other anti-epileptics and the GDG felt that a new review would be necessary prior to further evaluation, interpretation and decision-making regarding anti-epileptics in general. This will require assessment in future updates of the guidelines.

5. Management of Bone Pain

Some cancer pains are best treated with a combination of drug and non-drug measures. For example, radiation therapy, if available, should be considered in patients with metastatic bone pain, or pressure pain from localized cancer [17]. The European Society of Medical Oncology Clinical Practice Guidelines on Management of Cancer Pain recommends radiotherapy [105] and that all patients with pain from bone metastases which is proving difficult to be controlled by pharmacological therapy should be evaluated by a clinical oncologist for consideration of external beam radiotherapy or radioisotope treatment.

5.1 Bisphosphonates

Bisphosphonates inhibit osteoclast activity, and their use in cancer patients prevents the increased bone resorption common in metastatic bone disease. They thus can reduce complications or skeletal related events (SREs) and reduce bone pain and analgesic requirements.[106,107] Examples include clodronate, ibandronate, pamidronate, risendronate, etidronate, and zoledronate.

Recommendation

In adults (including older persons) and adolescents with bone metastases, a bisphosphonate should be used to prevent and treat bone pain. *(Strong recommendation; moderate quality evidence).*

Considerations

Clinicians should take into account the variable adverse renal effects of bisphosphonates before prescribing.

Summary of the evidence:

Bisphosphonates compared to placebo

Forty eligible trials compared bisphosphonates to placebo.[108-147]

Most trial participants had either breast or prostate cancer. Thirteen studies evaluated clodronate, nine zolendronate, five each ibandronate and pamidronate, and one each etidronate and risendronate. Studies were not explicit about what other drugs (including for pain relief) patients were on, but an informed assumption was made that the bisphosphonates were used as adjuvant therapies to treat or to prevent bone pain from metastases.

There is moderate strength of evidence of greater pain relief with use of bisphosphonates compared with placebo among patients with painful bone metastases. Seven trials evaluated categorical pain relief; however, four evaluated improvements in pain (e.g., reductions of at least 2 points on a 5 point pain scale)[116,126,136,144] and three evaluated complete pain relief.[113,123,134] Although favouring use of bisphosphonates, no statistically significant difference in complete relief of pain (RR 1.61; 95% CI 0.89, 2.93) or pain improvement (RR 1.24; 95% CI 0.90, 1.71) were found. Fourteen trials evaluated pain on continuous scales (which were each converted to a 100 point scale, with 100 = worst pain).[110,112,114-116,124,125,128,131,132,135,138,140,146] The studies, overall, indicated statistically significant improvement in pain, with an overall net difference of -11.8 (95% CI -17.6, -6.1).

No study evaluated speed of pain relief. A single trial provided low strength of evidence suggesting no significant difference in duration of pain relief between risendronate and placebo in people with prostate cancer. The study reported HR = 1.27 (95% CI 0.84, 1.92), favouring placebo (3.4 month median duration with risendronate, 5.5 months with placebo).

Five studies provide varying strength of evidence that bisphosphonates do not affect quality of life compared with placebo.[111,112,116,119,132] The studies evaluated clodronate (3 studies), ibandronate (1 study), and zolendronate (1 study). The five studies provided very low strength of evidence of no significant difference in changes in quality of life scores measured on a variety of scales (summary net difference on a 0 to 100 [best] scale = 8; 95% CI -6, 22). One study provided moderate strength of evidence of reduced and delayed deterioration in quality of life with clodronate (RR = 0.81; 95% CI 0.67, 0.99 and HR = 0.71; 95% CI 0.56, 0.92).[111]

Twenty-five trials evaluated the various skeletal-related events. [112,117,119-122,124,127,129,130,132,135,137,141,145-155] Overall, the trials provided moderate strength of evidence that bisphosphonates reduce the risk of skeletal-related events. The six studies that reported hazard ratios for time to first skeletal-related event (any) in comparisons of zolendronate (4 studies) or ibandronate (2 studies) found a statistically significant benefit of bisphosphonates over placebo (HR = 0.71; 95% CI 0.61, 0.84).[109,117,119,133,137,146] Eighteen trials found a reduction in risk of any skeletal-related event yielding a summary RR of 0.81 (95% CI 0.76, 0.86).[108,109,117-122,124,127,133,135,137-139,145-147] Four trials explicitly reported on the risk of osteonecrosis of the jaw.[110,126,133,143] Across the studies, there were no occurrences of this adverse event with either bisphosphonates (N=460) or placebo (N=450).

Choice of Bisphosphonates

Seven eligible studies compared different bisphosphonates in patients with various cancers with bone metastases—mostly breast, prostate, and non-small cell lung cancer. [154,156-161] The evidence is relatively sparse, with only seven studies evaluating four bisphosphonates: clodronate, ibandronate, pamidronate, and zoledronate. Study participants were generally older, with study mean ages ranging from 53 to 73 years old.

With only two or three studies evaluating pain control, there is low strength of evidence of no differences in relief of pain or mean changes in pain scores across the different bisphosphonates. From one study, pain relief on ibandronate (6%) was less common than on other bisphosphonates (15-26% in one or two studies for each drug). Changes in pain (as a continuous measure from 0 to 100 [worst]) were similar for each of the four bisphosphonates (-3.3 to -5.0).

Two studies provided very low strength of evidence regarding duration of pain relief. One study found no difference in average duration of pain relief in patients with a variety of cancers (about half with lung cancer) between ibandronate (5.5 months) and pamidronate (5.2 months).[158] One study reported that in patients with prostate cancer those taking clodronate had longer duration of pain relief (13 months) than those taking zolendronate (9 months, P=0.03).[159]

Six studies provided very low strength of evidence regarding skeletal-related events. Broadly similar percentages of people had any skeletal-related event across bisphosphonates (18-26%, no data on pamidronate). Within studies, fracture rates were mostly similar between bisphosphonates, except in one study of people with breast cancer in which 16% of those taking clodronate had fractures compared with 7% taking pamidronate (P=0.03). Three studies found no significant differences in rates of spinal cord compression across bisphosphonates. Two studies no significant differences in rates of bone radiotherapy across bisphosphonates. Three studies found no significant differences in rates of bone surgery across bisphosphonates.

Three studies reported on rates of hypercalcemia across bisphosphonates. Two of these found no differences in the incidence of hypercalcemia between ibandronate (10.7%) and zolendronate (9.3%),

and between clodronate (2.9%) and zolendronate (1.4%) respectively. The third trial reported that the hypercalcemia rate in the zolendronate group (28%) was lower compared with ibandronate (45%) (RR = 0.64; 95% CI 0.39, 1.03) and compared with pamidronate (50%)(RR = 0.57; 95% CI 0.35, 0.91).

Three studies reported rare rates of osteonecrosis of the jaw for clodronate (1.5%), ibandronate (0.7%), and zolendronate (1.2), providing low strength of evidence. No studies reported on quality of life.

Rationale

The GDG agreed that the balance of effect fell strongly in favour of prescribing bisphosphonates to appropriate populations compared with placebo. Osteonecrosis of the mandible, considered a serious adverse event, was deemed sufficiently rare (no cases were observed in the eligible trials; N=910), that the expected benefits outweighed the risks of harm. Clinicians might differ in their preferences for use of certain bisphosphonates, since there is evidence of differences in renal adverse effects and therefore the degree to which renal pathologies are be contraindications.[162]

The GDG believed that most patients would prefer bisphosphonates over placebo. However, they recognised that they are also expensive, often prohibitively so. The use of bisphosphonates in populations of older women with osteoporosis and in breast cancer patients with bone metastases has been deemed cost-saving or cost effective (depending on population) in a number of high income countries.[163-165] It remains to be seen whether these savings would apply to lower income settings.

Consideration was given to the issue that administration of the bisphosphonates should be IV, but this was not deemed to be a significant enough barrier to administration that the strength of the recommendation should be attenuated. The GDG thus made a strong recommendation in favour of bisphosphonates.

The GDG did not think patients would have major reasons to prefer one bisphosphonate to another and thought there would only be minor variability.

The GDG noted that all bisphosphonates are relatively expensive. In most settings, their use is often prohibitively expensive. The use of bisphosphonates in populations of older women with osteoporosis and in breast cancer patients with bone metastases has been deemed cost-saving or cost effective (depending on population) in a number of high income countries.[163-165] It remains to be seen whether these savings would apply to lower income settings. Most of the RCTs were conducted with intermittent intravenous administration. Using this method could be considered as a potential feasibility issue.

Combining these considerations, the GDG felt that equity could be affected in either direction. Taking into account the inconclusive evidence and other considerations, the GDG agreed that they could not make a recommendation of one bisphosphonate over another.

5.2. Monoclonal antibodies

Monoclonal antibodies to various targets, including osteoclasts and nerve growth factor, have been studied for management of bone pain due to cancer.

No Recommendation

WHO makes **no recommendation for or against** the use of monoclonal antibodies to prevent and treat bone pain.

Summary of the evidence

Monclonals compared to placebo

A single small trial compared monoclonals to placebo (see Annex 3, Evidence Profile 5.2.3). The study evaluated tanezumab in 59 adults with prostate cancer, breast cancer, renal cell carcinoma, or multiple myeloma with painful bone metastases (mean age 56 years, range 32 to 77).[166] The trial provided very low strength of evidence of no difference in average or worst pain between groups (between group differences -2.6 [95% CI -11.8, 6.6] and -0.1 [95% CI -9.3, 9.1], respectively), and in percentage of people who achieve pain relief (by at least 50%) (RR = 1.38 [95% CI 0.55, 3.49]). The trial did not report on speed of pain relief, duration of pain relief maintenance, quality of life, or functional outcomes. The trial provided very low strength of evidence regarding skeletal-related events, reporting only that 1 of 29 (3.4%) patients in the tanezumab arm had a femur fracture but, implicitly, none of the 30 people on placebo had a fracture (although one had undefined metastatic disease progression). No study reported on osteonecrosis of the jaw.

Choice of Monoclonals

No eligible trials were found comparing particular monoclonal antibodies over other monoclonal antibodies to prevent and treat bone pain.

Rationale

The GDG could not make a recommendation for or against monoclonal antibodies compared with placebo on the basis of one eligible trial. They noted that the paucity of trials probably derives from the preference to trial new therapies against the usual treatment rather than placebo.

The GDG also made no recommendation for or against the use of particular monoclonal antibodies over other monoclonal antibodies to prevent and treat bone pain.

5.3. Comparison of bisphosphonates or monoclonal antibodies

No Recommendation

WHO makes **no recommendation for or against** the comparative advantage of monoclonal antibodies over bisphosphonates to prevent and treat bone pain.

Summary of the evidence

Nine eligible trials compared monoclonal antibodies and bisphosphonates.[167-175] All evaluated the monoclonal denosumab; six evaluated zolendronate. Pamidronate and a variety of bisphosphonates (based on local practice) were also evaluated. Studies included patients with metastatic bone lesions, mostly from breast or prostate cancer, but also non-small cell lung cancer, multiple myeloma, and other cancers. Three trials with identical protocols[170-172] except for cancer inclusion criteria, were separately conducted and reported, but also combined and reported in a summary article.[175] Patient ages varied widely across studies. Studies were not explicit about what other drugs (including for pain relief) patients were on, but an informed assumption was made that the monoclonals and bisphosphonates were used as adjuvant therapies to treat or to prevent bone pain from metastases.

A single large trial of people with either breast cancer or multiple myeloma compared denosumab and zoledronate and provided low strength of evidence for no difference in pain relief (RR = 0.89; 95% CI 0.67, 1.10) and time until pain relief (speed) (HR = 1.02; 95% CI 0.91, 1.15), and very low strength of evidence for no difference in quality of life (RR = 1.08; 95% CI 0.95, 1.23).[174] No trial evaluated pain reduction maintenance.

Across six trials, there was high quality evidence that rates of any skeletal-related event (RR = 0.86; 95% CI 0.81, 0.91) and fracture (RR = 0.88; 95% CI 0.78, 0.96), bone radiation therapy (RR = 0.80; 95% CI 0.73, 0.88), and hypercalcemia (RR = 0.58; 95% CI 0.34, 0.81) were statistically significantly more common among those treated with bisphosphonates. Two trials provided low strength of evidence for functional outcomes. Three trials provide high strength of evidence that the risk of osteonecrosis of the jaw is higher with denosumab than bisphosphponates, with a summary RR = 1.40 (95% CI 0.92, 2.13).

Rationale

The systematic review evidence suggests that monoclonals reduce the risk of skeletal-related events and may improve functional outcomes more than bisphosphonates, but increase the risk of osteonecrosis of the jaw. The choice of monoclonals or bisphosphonates may make little or no difference to bone pain, or time to pain relief. Monoclonal antibody regimens involve a lower medicine-administration burden than bisphosphonates, which patients would prefer but monoclonals have a significantly higher cost. Osteonecrosis of necrosis of the jaw (higher with monoclonal antibodies) is an outcome sufficiently adverse that the GDG believed it could affect patient preferences, but its expected disutility to patients must be weighed against the expected disutility of skeletal-related events which is higher with bisphosphonates.

Although there are relative benefits to the use of denosumab compared with bisphosphonates, the relative cost of denosumab is disproportionate to the benefits. The GDG agreed that they could not recommend one medicine category over the other on these grounds.

5.4. Single dose radiotherapy compared with high-fractionated radiotherapy

Radiotherapy is used to reduce analgesic requirements, improve quality of life, and maintain or improve skeletal function by mitigating the risk of pathological fractures and spinal cord compression. Palliative radiotherapy is indicated for bone pain after the appearance of a new painful site and after insufficient beneficial effect from an initial radiotherapy treatment.[176]

Recommendation

In adults (including older persons) and adolescents with pain related to bone metastases, single-dose radiotherapy should be used when radiotherapy is indicated and available. *(Strong recommendation; high quality evidence)*

Remarks

7. This recommendation applies to people who already have painful metastases; it is not a recommendation concerning preventive radiotherapy.

Considerations

Use of single dose radiotherapy probably has beneficial effects on treatment coverage, waiting times, and financial savings.

Summary of the evidence

Twenty-three eligible RCTs compared low-fractioned to high-fractioned radiotherapy (See Annex 3, Evidence Profile 6.1).[177-200] Almost all used a single fractionation of 8 Gy in the low fractionation arms (two older studies used single fractionations of either 10 Gy or a range from 8 to 15 Gy; one study arm that used 5 Gy was omitted). High-fractionated radiotherapy ranged from 20 to 30 Gy mostly given over 5 to 10 fractions. These trials included patients with a variety of cancer types, with breast, prostate, and lung cancers included in most trials. Among trials that reported participant ages, study participants were mostly older adults; the mean age ranged from 48 to 72 years old, with the youngest participant being 16 years old.

There is high quality evidence that the different fractionation schedules were similarly effective in terms of producing pain relief and improvement. Under both schedules, 25% or 26% of participants achieved complete pain relief (RR = 0.97; 95% CI 0.89, 1.06) and 69% or 71% of participants achieved either complete or partial pain relief (RR = 0.97; 95% CI 0.93, 0.998). Pain relief was infrequently reported on a continuous scale. Three trials provided low quality evidence of no difference between fractionation schedules. The trials could not be quantitatively combined, but all reported statistically non-significant differences.

Three studies reported on pain relief speed (time to complete response), providing moderate strength of no difference between radiotherapy schedules; however, all studies reported outcomes vaguely, either as survival curves showing nonsignificant differences or that pain relief was achieved in two weeks in both study arms. Nine studies reported on duration of pain relief (pain reduction maintenance), providing moderate quality evidence of no difference between radiotherapy schedules. Most studies reported no significant difference between radiotherapy schedules without providing data; one trial reported an HR = 0.91 (95% CI 0.46, 1.82).

There is high quality evidence that pathological fractures at the treatment (index) site are more common with low-fractionated than high-fractionated radiotherapy. Across studies about 3% to 4% of patients had a pathological fracture at the index site and the RR = 1.48 (95% CI 1.08, 2.03). There is high quality evidence that spinal cord compression (among those treated for spinal metastases) are

more common with low-fractionated (2.2%) than high-fractionated radiotherapy (1.4%); although the difference was not statistically significant. Across studies, the RR = 1.45; 95% CI 0.89, 2.37).

Rationale

The GDG agreed that there was no difference in benefit between low-fractionated (single dose) or high-fractionated (multiple dose) radiotherapy with respect to the critical outcomes of bone pain relief, speed, or duration of pain relief. The GDG recognised that there was high quality evidence that the important outcome of risk of fracture at the treatment site was greater in those receiving low fractionated radiotherapy compared to high-fractionated (multiple dose) radiotherapy.

The GDG observed that there was likely to be minor variabiity among patient values and preferences with regard to low fractionated therapy with less trips to receive treatment an advantage. Similarly, there was likely to be minor variability in acceptability among healthcare workers for providing single dose radiotherapy. Low-fractionated radiotherapy - where a patient receives a larger single dose (e.g. a 8Gy fraction) in a single clinic visit - is less expensive in terms of both time and money than a longer schedule where a patient receives smaller individual doses but an overall greater amount of radiotherapy split over several visits (e.g. 20-30 Gy given over 5-10 fractions).[201] Therefore the GDG established that the negligible clinical differences between the schedules with respect to pain, coupled with the large cost and equity benefits of single-fractionated radiotherapy, favoured single dose over multiple dose radiotherapy where indicated despite the increase in fracture risk. If more patients were to be given single dose therapy, in settings where there is a shortage of radiation equipment and staff, the same resources could be used for greater coverage, as well as having lower costs to patients such as travel, making the single dose option the most feasible. For these reasons and the high quality evidence, the recommendation was strong.

5.5. Radioisotopes for bone pain

Radioisotopes are sometimes administered for diffuse bone pain that cannot be treated with radiotherapy.

No Recommendation

WHO makes **no recommendation for or against** the use of radioisotopes in adults and adolescents with pain related to bone metastases for achieving pain control.

Summary of the evidence

Three RCTs compared radioisotopes to a control arm that did not use radioisotopes.[119,202,203] All three trials were conducted in men with prostate cancer. The studies evaluated Strontium-89 (2 trials) and Samarium-153 (1 trial). Trial participants were mostly older adults; the mean age ranged from 69 to 71 years. A single very small trial of 24 participants provided very low quality of evidence of better bone pain relief with radioisotope treatment (RR = 21; 1.37, 322) and a net difference in bone pain on VAS of -38 points (95% CI -47, -29) (low quality of evidence). No trial reported pain relief speed or pain reduction maintenance.

Two trials provided high quality of evidence that skeletal-related events were less common after radioisotope threament than placebo (RR = 0.86; 95% CI 0.77, 0.95) and that skeletal-related events were delayed among those who had received radioisotopes compared with placebo (HR = 0.73; 95% CI 0.62, 0.86). The two trials provided low quality of evidence of similar risk of fracture (RR = 1.05; 95% CI 0.53, 2.08) and spinal cord compression (RR = 0.82; 95% CI 0.39, 1.71). One trial provided moderate

quality of evidence of fewer episodes of bone pain (reported as an adverse event) with radiotherapy (RR = 0.81; 95% CI 0.71, 0.91). One study provided very low quality of evidence of no significant differences in improvements in quality of life (RR = 0.97; 95% CI 0.68, 1.24),

Rationale

The GDG noted that in patients with prostate cancer, use of radioisotopes reduces and delays skeletal-related events, probably improves quality of life, and may provide greater bone pain relief. However, GDG selected not to make a recommend for or against the use of radioisotopes due to their prohibitive cost and the lack of generalizbility of the current evidence, which was drawn only from men with prostate cancer.

Research agenda

In general, despite decades of research into cancer pain management, the evidence was scant or lacking for several critical clinical questions limiting development of recommendations in these areas.

Differences in trial protocols, differences in the measurement of pain outcomes, and significant heterogeneity among trial participants limited opportunities to pool results using meta-analysis. It would be helpful for building evidence continuously if assessment and measurement of pain is standardised in future cancer pain management trials to allow for statistical data synthesis. For example, a validated scale maybe endorsed by country associations and recommended for use in clinical practice and research.

The risk of bias was noted to be high across many trials. Future trials should conform to standard RCT methods and investigators need to ensure that methodological quality is not compromised during the conduct of the trial. The CONSORT statement provides a useful template for reporting clinical trials.[204]

Clinical trial evidence was absent or very limited for the use of several adjuvant therapies including choice of corticosteroid, and for anti-convulsants and anti-depressants, despite these being part of established practice for cancer pain management. Trial research is urgently needed to address the clinical uncertainty apparent in this area. Trial data may provide supportive data to recommend the practice, or importantly, indicate if there is no benefit, or indeed harm, allowing for amendment of current clinical protocols to reduce unnecessary cost and avoid potential harms. Outcomes should include efficacy, safety and pharmaco-economic outcomes. Comparisons should not only be against placebo, but also against analgesics as well as other medicines.

Like many fields, most trials were conducted in high-income settings. Research on cancer pain management should be prioritised in low- and middle-income countries where cancer is increasing significantly. As outlined in the Lancet Commission Report on Palliative Care and Pain Relief, trial investigators may wish to measure serious health-related suffering as an outcome, and evaluate an essential, affordable package of palliative care and pain relief interventions.[205] The latter may be best assessed using an implementation science approach and pragmatic trial study design. Studies on the optimal route of administration for opioids and cost-effectiveness studies thereof, are also required.

Research on opioids should take into account the ongoing opioid crisis in North America and evaluate the risk for substance misuse in all trials of opioid use across different settings. Evidence-based protocols for opioid cessation should be evaluated in patients with cancer pain who no longer require pain management in order to better guide cancer pain clinicians in this area.

A global landscape analysis of the effects of restrictive legislation and regulations (including the negative effects of barriers to adequate access to opioids) will be helpful. Such an analysis may include an evaluation of the reasons why in some countries, opioids are available but have not led to an opioid crisis of the scale observed in North America (such as in some European countries).

The use of cannabinoids was not included as a PICO in this guidelines process, but is currently being widely investigated for both chronic non-cancer and cancer-related pain and trials and syntheses of current data of cannabinoids for cancer pain are warranted.

Interests declared by persons involved in guideline development

For full details of these declared interests and GDG and ERG member characteristics, please see Annex 4 'Background to the Development of the Guidelines & Details of Personnel'. Of the invited experts who became GDG members, none declared potential conflicts of interest that were deemed to require specific management in GDG meetings or during the guideline development process.

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*Jim Cleary, representing the University of Wisconsin-Madison Pain and Policies Studies Group was an observer at the first scoping meeting. He then joined the GDG where he represented himself, as is the case for other GDG members present from the start.

**Eric Krakauer first joined the guideline development process as a member of the WHO Steering Committee, and post-departure from WHO joined the GDG representing himself.

References

1. World Health Organization. World Cancer Report 2014 (ePUB) (World Health Organisation, Geneva, 2014).
2. van den Beuken-van Everdingen, M.H., Hochstenbach, L.M., Joosten, E.A., Tjan-Heijnen, V.C. & Janssen, D.J. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* **51**, 1070-1090 e1079 (2016).
3. International Association for the Study of Pain (IASP). International Association for the Study of Pain (IASP) taxonomy. Vol. 2018 24 (1994).
4. Haun, M.W*., et al.* Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev* **6**, CD011129 (2017).
5. Knaul, F.M*., et al.* Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report. *The Lancet*, Online (2017).
6. United Nations General Assembly. International Covenant on Economic, Social and Cultural Rights. (1966, entry into force 1976).
7. United Nations, E.a.S.C. Single Convention on Narcotic Drugs of 1961, as amended by the 1972 protocol.
8. World Health Assembly. Resolution 67.19 Strengthening of palliative care as a component of comprehensive care throughout the life course. (2014).
9. Seya, M.-J., Gelders, S.F.A.M., Achara, O.U., Barbara, M. & Scholten, W.K. A First Comparison Between the Consumption of and the Need for Opioid Analgesics at Country, Regional, and Global Levels. *Journal of Pain & Palliative Care Pharmacotherapy* **25**, 6-18 (2011).
10. World Health Organization. WHO Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. (2010).
11. Sharkey, L., Loring, B., Cowan, M., Riley, L. & Krakauer, E.L. National palliative care capacities around the world: Results from the World Health Organization Noncommunicable Disease Country Capacity Survey. *Palliat Med* **32**, 106-113 (2018).
12. Manchikanti, L*., et al.* Opioid epidemic in the United States. *Pain Physician* **15**, ES9-38 (2012).
13. Centers for Disease Control and Prevention. Opioid overdose: understanding the epidemic. Vol. 2018.
14. Haffajee, R.L. & Mello, M.M. Drug Companies' Liability for the Opioid Epidemic. *N Engl J Med* **377**, 2301-2305 (2017).
15. Manchikanti, L., Kaye, A.M. & Kaye, A.D. Current State of Opioid Therapy and Abuse. *Current pain and headache reports* **20**, 34 (2016).
16. Häuser, W., Petzke, F., Radbruch, L. & Tölle, T.R. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: a transatlantic perspective. *Pain Management* **6**, 249-263 (2016).
17. World Health Organization. Cancer Pain Relief. (1986).
18. World Health Organization. *Cancer Pain Relief, 2nd Ed. With a guide to opioid availability.*, (WHO, Geneva, 1996).
19. World Health Organization. Cancer Pain Relief and Palliative Care in Children. (1998).
20. Vargas-Schaffer, G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Canadian family physician Medecin de famille canadien* **56**, 514-517, e202-515 (2010).
21. Schmidt-Hansen, M., Bromham, N., Taubert, M., Arnold, S. & Hilgart, J.S. Buprenorphine for treating cancer pain. *Cochrane Database Syst Rev*, CD009596 (2015).
22. Skaer, T.L. Transdermal opioids for cancer pain. *Health and quality of life outcomes* **4**, 24 (2006).
23. Leppert, W. & Luczak, J. The role of tramadol in cancer pain treatment--a review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* **13**, 5-17 (2005).
24. Rubin, G*., et al.* The expanding role of primary care in cancer control. *Lancet Oncol* **16**, 1231-1272 (2015).
25. Mills, S., Torrance, N. & Smith, B.H. Identification and Management of Chronic Pain in Primary Care: a Review. *Current psychiatry reports* **18**, 22 (2016).
26. Krakauer, E.L., Wenk, R., Buitrago, R., Jenkins, P. & Scholten, W. Opioid inaccessibility and its human consequences: reports from the field. *J Pain Palliat Care Pharmacother* **24**, 239-243 (2010).
27. World Health Organization. Ensuring balance in national policies on controlled substances: Guidance for availability and accessibility of controlled medicines. (2011).

28. Jacox, A., Carr, D.B. & Payne, R. New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med* **330**, 651-655 (1994).
29. Graham, G.G., Davies, M.J., Day, R.O., Mohamudally, A. & Scott, K.F. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* **21**, 201-232 (2013).
30. Cherny NI, Fallon MT, Kaasa S, Portenoy RK & (eds)., C.D. *Oxford Textbook of Palliative Medicine*, (Oxford University Press, Oxford, 2015).
31. Bandieri, E.*, et al.* Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. *J Clin Oncol* **34**, 436-442 (2016).
32. Strobel, E. [Drug therapy in severe tumor pain. Comparative study of a new combination preparation versus diclofenac-Na]. *Fortschr Med* **110**, 411-414 (1992).
33. Zecca, E.*, et al.* Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial. *J Pain Symptom Manage* **52**, 783-794 e786 (2016).
34. Riley, J.*, et al.* Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. *J Pain Symptom Manage* **49**, 161-172 (2015).
35. Corli, O., Floriani, I., Roberto, A. & al., e. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Annals of oncology : official journal of the European Society for Medical Oncology* **27**, 1107-1115 (2016).
36. Ahmedzai, S. & Brooks, D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* **13**, 254-261 (1997).
37. Arkinstall, W.W., Goughnour, B.R., White, J.A. & Stewart, J.H. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. *CMAJ* **140**, 653-657, 661 (1989).
38. Beaver, W.T., Wallenstein, S.L., Houde, R.W. & Rogers, A. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. *Clin Pharmacol Ther* **8**, 415-426 (1967).
39. Broomhead, A.*, et al.* Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *J Pain Symptom Manage* **14**, 63-73 (1997).
40. Bruera, E.*, et al.* Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol* **16**, 3222-3229 (1998).
41. Chen YZ, W., Liang, H. & Wu, G. The analgesic effect of ibuprofen-codeine sustained release tablets on postoperative and cancer pain. *Chinese Journal of Clinical Rehabilitation* **7**, 1290-1291 (2003).
42. Finn, J.*, et al.* Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **11**, 967-972 (1993).
43. Gabrail, N.Y., Dvergsten, C. & Ahdieh, H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. *Curr Med Res Opin* **20**, 911-918 (2004).
44. Hagen, N.A. & Babul, N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer* **79**, 1428-1437 (1997).
45. Hanna, M., Thipphawong, J. & Study, G. A randomized, double-blind comparison of OROS(R) hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC Palliat Care* **7**, 17 (2008).
46. Heiskanen, T. & Kalso, E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* **73**, 37-45 (1997).
47. Homsi, J.*, et al.* A comparative study of 2 sustained-release morphine preparations for pain in advanced cancer. *Am J Hosp Palliat Care* **27**, 99-105 (2010).
48. Kalso, E. & Vainio, A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther* **47**, 639-646 (1990).
49. Klepstad, P., Kaasa, S., Jystad, A., Hval, B. & Borchgrevink, P.C. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain* **101**, 193-198 (2003).

50. Koch, A.*, et al.* Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: a double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group. *Eur J Cancer* **47**, 1546-1555 (2011).
51. Kress, H.G.*, et al.* Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. *Eur J Pain* **20**, 1513-1518 (2016).
52. Marinangeli, F.*, et al.* Improved cancer pain treatment using combined fentanyl-TTS and tramadol. *Pain practice : the official journal of World Institute of Pain* **7**, 307-312 (2007).
53. Mercadante, S.*, et al.* Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **16**, 3656-3661 (1998).
54. Minotti, V.*, et al.* A double-blind study comparing two single-dose regimens of ketorolac with diclofenac in pain due to cancer. *Pharmacotherapy* **18**, 594-508 (1998).
55. Mucci-LoRusso, P.*, et al.* Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain* **2**, 239-249 (1998).
56. Pannuti, F., Robustelli della Cuna, G., Ventaffrida, V., Strocchi, E. & Camaggi, C.M. A double-blind evaluation of the analgesic efficacy and toxicity of oral ketorolac and diclofenac in cancer pain. The TD/10 recordati Protocol Study Group. *Tumori* **85**, 96-100 (1999).
57. Poulain, P. A study to evaluate the effectiveness and safety of CG5503 (tapentadol) in the treatment of chronic tumor-related pain compared with placebo and morphine. *ClinicalTrialsgov*, NCT00505414 (2010).
58. Rodríguez, M.*, et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered dexketoprofen trometamol and ketorolac in bone cancer pain. *Pain* **104**, 103-110 (2003).
59. Ventafridda, V., Ripamonti, C., Bianchi, M., Sbanotto, A. & De Conno, F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage* **1**, 203-207 (1986).
60. Walsh, T.D.*, et al.* A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. *Am J Clin Oncol* **15**, 268-272 (1992).
61. Wilder-Smith, C.H., Schimke, J., Osterwalder, B. & Senn, H.J. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* **5**, 141-146 (1994).
62. Wong, J.O., Chiu, G.L., Tsao, C.J. & Chang, C.L. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sin* **35**, 25-32 (1997).
63. Dellemijn, P.L., Verbiest, H.B., van Vliet, J.J., Roos, P.J. & Vecht, C.J. Medical therapy of malignant nerve pain. A randomised double-blind explanatory trial with naproxen versus slow-release morphine. *Eur J Cancer* **30a**, 1244-1250 (1994).
64. Moertel, C.G., Ahmann, D.L., Taylor, W.F. & Schwartau, N. Aspirin and pancreatic cancer pain. *Gastroenterology* **60**, 552-553 (1971).
65. Staquet, M., Gantt, C. & Machin, D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther* **23**, 397-401 (1978).
66. Staquet, M., Luyckx, A. & Van Cauwenberge, H. A double-blind comparison of alclofenac, pentazocine, and codeine with placebo control in pathologic pain. *The Journal of clinical pharmacology and new drugs* **11**, 450-455 (1971).
67. Staquet, M. & Renaud, A. Double-blind, randomized trial of piroxicam and codeine in cancer pain. *Current Therapeutic Research* **53**, 435-440 (1993).
68. Minotti, V.*, et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* **74**, 133-137 (1998).
69. Bauer, M., Schmid, H. & Schulz-Wentland, R. Gynecologic carcinoma patients with chronic pain. Comparison of sublingual buprenorphine with tilidine plus naloxone. *Therapiewoche* **35**, 3943-3947 (1985).
70. Poulain, P.*, et al.* Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. *J Pain Symptom Manage* **36**, 117-125 (2008).
71. Ferrer-Brechner, T. & Ganz, P. Combination therapy with ibuprofen and methadone for chronic cancer pain. *Am J Med* **77**, 78-83 (1984).
72. Sittl, R., Griessinger, N. & Likar, R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a

multicenter, randomized, double-blind, placebo-controlled trial. *Clinical therapeutics* **25**, 150-168 (2003).
73. Rodriguez, M*., et al.* Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. *Eur J Cancer* **30a**, 584-587 (1994).
74. Xiao, Y*., et al.* Clinical study on fluvoxamine combined with oxycodone prolonged-release tablets in treating patients with moderate to severe cancer pain. *Asian Pac J Cancer Prev* **15**, 10445-10449 (2014).
75. Rodriguez, R*., et al.* Incidence of weak opioids adverse events in the management of cancer pain: a double-blind comparative trial. *Journal of palliative medicine* **10**, 56-60 (2007).
76. Kress, H.G*., et al.* Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain. *Pain Physician* **17**, 329-343 (2014).
77. Portenoy, R.K.H., NA. Breakthrough pain: definition, prevalence and characteristics. in *Pain*, Vol. 41 273-281 (1990).
78. Mercadante, S. & Bruera, E. Opioid switching: A systematic and critical review. *Cancer Treatment Reviews* **32**, 304-315 (2006).
79. Caraceni, A*., et al.* Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* **13**, e58-68 (2012).
80. Knudsen, J., Mortensen, S.M., Eikard, B. & Henriksen, H. [Morphine depot tablets compared with conventional morphine tablets in the treatment of cancer pain]. *Ugeskr Laeger* **147**, 780-784 (1985).
81. Thirlwell, M.P*., et al.* Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* **63**, 2275-2283 (1989).
82. Cundiff, D*., et al.* Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. *Cancer* **63**, 2355-2359 (1989).
83. Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A. & De Conno, F. Clinical observations on controlled-release morphine in cancer pain. *J Pain Symptom Manage* **4**, 124-129 (1989).
84. Hanks, G.W., Twycross, R.G. & Bliss, J.M. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. *Anaesthesia* **42**, 840-844 (1987).
85. Gourlay, G.K*., et al.* Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain* **69**, 295-302 (1997).
86. Gillette, J*., et al.* Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. *Clinical Drug Investigation* **14**, 22-27 (1997).
87. Walsh, T. Clinical evaluation of slow release morphine tablets. *Advances in Pain Research and Therapy* **9**, 727-731 (1985).
88. Moulin, D.E., Kreeft, J.H., Murray-Parsons, N. & Bouquillon, A.I. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet; Feb 23 1991.* **337**, 465-468. (1991).
89. Gowing, L., Ali, R., White, J.M. & Mbewe, D. Buprenorphine for managing opioid withdrawal. *Cochrane Database Syst Rev* **2**, CD002025 (2017).
90. Amato, L*., et al.* Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev*, CD003409 (2013).
91. Bruera, E. & Watanabe, S. Corticosteroids as adjuvant analgesics. *J Pain Symptom Manage*, 9(7):442-445. (1994).
92. Bruera, E., Roca, E., Cedaro, L., Carraro, S. & Chacon, R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* **69**, 751-754 (1985).
93. Popiela, T., Lucchi, R. & Giongo, F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. *European journal of cancer & clinical oncology* **25**, 1823-1829 (1989).
94. Twycross, R.G. & Guppy, D. Prednisolone in terminal breast and bronchogenic cancer. *Practitioner* **229**, 57-59 (1985).
95. Della Cuna, G.R., Pellegrini, A. & Piazzi, M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. *Eur J Cancer Clin Oncol* **25**, 1817-1821 (1989).
96. Bruera, E*., et al.* Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage* **28**, 381-388 (2004).

97. Yennurajalingam, S.*, et al.* Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol* **31**, 3076-3082 (2013).
98. Paulsen, O.*, et al.* Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **32**, 3221-3228 (2014).
99. Mishra, S., Bhatnagar, S., Goyal, G.N., Rana, S.P. & Upadhya, S.P. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* **29**, 177-182 (2012).
100. Fallon, M.T. Neuropathic pain in cancer. *Br J Anaesth* **111**, 105-111 (2013).
101. Vedula, S.S., Bero, L., Scherer, R.W. & Dickersin, K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *New England Journal of Medicine*, 361(320):1963–1971. (2009).
102. Vedula, S.S., Goldman, P.S., Rona, I.J., Greene, T.M. & Dickersin, K. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin litigation. *Trials* **13**, 136 (2012).
103. Vedula, S.S., Li, T. & Dickersin, K. Differences in reporting of analyses in internal company documents versus published trial reports: comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLoS Med* **10**, e1001378 (2013).
104. Dickersin, K. Reporting and other biases in studies of Neurontin for migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain. in *Researchgate* (2008).
105. Ripamonti, C.I., Santini, D., Maranzano, E., Berti, M. & Roila, F. Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann Oncol* **23 Suppl 7**, vii139-154 (2012).
106. Wong, R. & Wiffen, P.J. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev*, CD002068 (2002).
107. Hoskin, P.*, et al.* A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. *J Natl Cancer Inst* **107**, 107(110) pii: djv197. (2015).
108. Body, J.J.*, et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* **14**, 1399-1405 (2003).
109. Body, J.J.*, et al.* Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *Br J Cancer* **90**, 1133-1137 (2004).
110. Broom, R.J.*, et al.* Everolimus and zoledronic acid in patients with renal cell carcinoma with bone metastases: a randomized first-line phase II trial. *Clin Genitourin Cancer* **13**, 50-58 (2015).
111. Dearnaley, D.P.*, et al.* A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *J Natl Cancer Inst* **95**, 1300-1311 (2003).
112. Diel, I.*, et al.* Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *European journal of cancer (Oxford, England : 1990)* **40**, 1704-1712 (2004).
113. Elomaa, I.*, et al.* Effect of oral clodronate on bone pain. A controlled study in patients with metastic prostatic cancer. *Int Urol Nephrol* **24**, 159-166 (1992).
114. Ernst, D.S.*, et al.* A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* **13**, 319-326 (1997).
115. Ernst, D.S.*, et al.* A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *J Pain Symptom Manage* **7**, 4-11 (1992).
116. Ernst, D.S.*, et al.* Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* **21**, 3335-3342 (2003).
117. Heras, P., Kritikos, K., Hatzopoulos, A. & Georgopoulou, A.P. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. *Eur J Cancer Care (Engl)* **18**, 653-656 (2009).
118. Hortobagyi, G.N.*, et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* **335**, 1785-1791 (1996).
119. James, N.*, et al.* TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony

metastatic castration-refractory prostate cancer. *Health technology assessment (Winchester, England).* **20**, 1-288 (2016).
120. Kanis, J.A., Powles, T., Paterson, A.H., McCloskey, E.V. & Ashley, S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* **19**, 663-667 (1996).
121. Kohno, N.*, et al.* Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **23**, 3314-3321 (2005).
122. Kristensen, B.*, et al.* Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* **246**, 67-74 (1999).
123. Kylmala, T.*, et al.* Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group. *Eur J Cancer* **29A**, 821-825 (1993).
124. Lipton, A.*, et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* **88**, 1082-1090 (2000).
125. Martoni, A.*, et al.* Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. *Oncology* **48**, 97-101 (1991).
126. Meulenbeld, H.*, et al.* Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). *European journal of cancer (Oxford, England : 1990)* **48**, 2993-3000 (2012).
127. Murakami, H.*, et al.* Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group. *Cancer Sci* **105**, 989-995 (2014).
128. O'Rourke, N., McCloskey, E., Houghton, F., Huss, H. & Kanis, J.A. Double-blind, placebo-controlled, dose-response trial of oral clodronate in patients with bone metastases. *J Clin Oncol* **13**, 929-934 (1995).
129. Pan, Y.*, et al.* Docetaxel with or without zoledronic acid for castration-resistant prostate cancer. *International urology and nephrology* **46**, 2319-2326 (2014).
130. Paterson, A.H.*, et al.* Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* **11**, 59-65 (1993).
131. Piga, A.*, et al.* A double blind randomized study of oral clodronate in the treatment of bone metastases from tumors poorly responsive to chemotherapy. *J Exp Clin Cancer Res* **17**, 213-217 (1998).
132. Robertson, A.G., Reed, N.S. & Ralston, S.H. Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. *J Clin Oncol* **13**, 2427-2430 (1995).
133. Rosen, L.S.*, et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* **21**, 3150-3157 (2003).
134. Siris, E.S., Hyman, G.A. & Canfield, R.E. Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. *Am J Med* **74**, 401-406 (1983).
135. Small, E.J., Smith, M.R., Seaman, J.J., Petrone, S. & Kowalski, M.O. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* **21**, 4277-4284 (2003).
136. Smith, J., Jr. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study. *The Journal of urology* **141**, 85-87 (1989).
137. Smith, M.R.*, et al.* Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). *J Clin Oncol* **32**, 1143-1150 (2014).
138. Theriault, R.L.*, et al.* Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* **17**, 846-854 (1999).
139. Tripathy, D.*, et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* **15**, 743-750 (2004).
140. Tubiana-Hulin, M.*, et al.* [Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases]. *Bull Cancer* **88**, 701-707 (2001).

141. Ueno, S.*, et al.* Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. *Anticancer Res* **33**, 3837-3844 (2013).
142. van Holten-Verzantvoort, A.T.*, et al.* Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* **2**, 983-985 (1987).
143. van Holten-Verzantvoort, A.T.*, et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* **11**, 491-498 (1993).
144. Vinholes, J., Purohit, O., Abbey, M., Eastell, R. & Coleman, R. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Annals of oncology : official journal of the European Society for Medical Oncology* **8**, 1243-1250 (1997).
145. Wang, Y., Tao, H., Yu, X., Wang, Z. & Wang, M. Clinical significance of zoledronic acid and strontium-89 in patients with asymptomatic bone metastases from non-small-cell lung cancer. *Clin Lung Cancer* **14**, 254-260 (2013).
146. Zaghloul, M.S.*, et al.* A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *Int J Clin Oncol* **15**, 382-389 (2010).
147. Zarogoulidis, K.*, et al.* The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. *Int J Cancer* **125**, 1705-1709 (2009).
148. Theriault, R.*, et al.* Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **17**, 846-854 (1999).
149. Rosen, L.*, et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **21**, 3150-3157 (2003).
150. Hortobagyi, G.*, et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *The New England journal of medicine* **18**, 1785-1791 (1996).
151. Body, J.*, et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Annals of oncology : official journal of the European Society for Medical Oncology* **14**, 1399-1405 (2003).
152. Body, J.*, et al.* Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. *British journal of cancer* **90**, 1133-1137 (2004).
153. van Holten-Verzantvoort, A.*, et al.* Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* **2**, 983-985 (1987).
154. Rosen, L.*, et al.* Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* **100**, 36-43 (2004).
155. van Holten-Verzantvoort, A.*, et al.* Palliative pamidronate treatment in patients with bone metastases from breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **11**, 491-498 (1993).
156. Body, J., Lichinitser, M., Tjulandin, S., Garnero, P. & Bergstrom, B. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. *Annals of oncology : official journal of the European Society for Medical Oncology* **18**, 1165-1171 (2007).
157. Francini, F.*, et al.* Effects of intravenous zoledronic acid and oral ibandronate on early changes in markers of bone turnover in patients with bone metastases from non-small cell lung cancer. *Int J Clin Oncol* **16**, 264-269 (2011).
158. Choudhury, K.B.*, et al.* A randomized controlled trial to compare the efficacy of bisphosphonates in the management of painful bone metastasis. *Indian J Palliat Care* **17**, 210-218 (2011).
159. Wang, F.*, et al.* Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases. *Medical oncology (Northwood, London, England)* **30**, 657 (2013).
160. Barrett-Lee, P.*, et al.* Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. *Lancet Oncol* **15**, 114-122 (2014).

161. von Au, A.*, et al.* Intravenous pamidronate versus oral and intravenous clodronate in bone metastatic breast cancer: a randomized, open-label, non-inferiority Phase III trial. *Onco Targets Ther* **9**, 4173-4180 (2016).
162. Toussaint, N.D., Elder, G.J. & Kerr, P.G. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol* **4**, 221-233 (2009).
163. Botteman, M.*, et al.* Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. *Ann Oncol* **17**, 1072-1082 (2006).
164. Fleurence, R.L., Iglesias, C.P. & Johnson, J.M. The cost effectiveness of bisphosphonates for the prevention and treatment of osteoporosis: a structured review of the literature. *Pharmacoeconomics* **25**, 913-933 (2007).
165. Lippuner, K., Pollock, R.F., Smith-Palmer, J., Meury, T. & Valentine, W.J. A review of the cost effectiveness of bisphosphonates in the treatment of post-menopausal osteoporosis in Switzerland. *Appl Health Econ Health Policy* **9**, 403-417 (2011).
166. Sopata, M.*, et al.* Efficacy and safety of tanezumab in the treatment of pain from bone metastases. *Pain* **156**, 1703-1713 (2015).
167. Body, J.J.*, et al.* A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* **12**, 1221-1228 (2006).
168. Lipton, A.*, et al.* Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research* **14**, 6690-6696 (2008).
169. Fizazi, K.*, et al.* Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* **27**, 1564-1571 (2009).
170. Stopeck, A.T.*, et al.* Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* **28**, 5132-5139 (2010).
171. Henry, D.H.*, et al.* Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* **29**, 1125-1132 (2011).
172. Fizazi, K.*, et al.* Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* **377**, 813-822 (2011).
173. Martin, M.*, et al.* Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. *Clin Cancer Res* **18**, 4841-4849 (2012).
174. Cleeland, C.S.*, et al.* Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* **119**, 832-838 (2013).
175. Lipton, A.*, et al.* Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer* **48**, 3082-3092 (2012).
176. De Felice, F., Piccioli, A., Musio, D. & Tombolini, V. The role of radiation therapy in bone metastases management. *Oncotarget* **8**, 25691-25699 (2017).
177. Altundağ, M.B., Üçer, A.R., Çalikoğlu, T. & Güran, Z. Single (500 cGy, 800 cGy) and multifraction (300x10 cGy) radiotherapy schedules in the treatment of painful bone metastases. *THOD Turk Hematol.-Onkol. Derg.* **12**, 16-21 (2002).
178. Amouzegar-Hashemi, F., Behrouzi, H., Kazemian, A., Zarpak, B. & Haddad, P. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. *Curr Oncol.* **15**, 151. (2008).
179. Anter, A.H. Single Fraction versus Multiple Fraction Radiotherapy for treatment of painful bone metastases: A Prospective Study; Mansoura experience. *Forum of Clinical Oncology* **6**, 8-13 (2015).
180. Badzio, A.*, et al.* 20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study. **53**, 261-264 (2003).
181. Bone Pain Trial Working, P. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. *Radiother Oncol* **52**, 111-121 (1999).
182. Chow, E.*, et al.* Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol* **15**, 164-171 (2013).

183. Foro Arnalot, P*., et al.* Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **89**, 150-155 (2008).
184. Gaze, M.N*., et al.* Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol.* **45**, 109-116. (1997).
185. Gutierrez Bayard, L., Salas Buzon Mdel, C., Angulo Pain, E. & de Ingunza Baron, L. Radiation therapy for the management of painful bone metastases: Results from a randomized trial. *Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology* **19**, 405-411 (2014).
186. Hamouda, W.E., Roshdy, W. & Teema, M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. *Gulf J Oncolog.* **1**, 35-41. (2007).
187. Hartsell, W.F*., et al.* Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *Journal of the National Cancer Institute* **97**, 798-804 (2005).
188. Kagei, K*., et al.* [A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report]. *Gan No Rinsho.* **36**, 2553-2558. (1990).
189. Koswig, S. & Budach, V. Remineralisation und Schmerzlinderung von Knochenmetastasen nach unterschiedlich fraktionierter Strahlentherapie (10mal 3 Gy vs. 1mal 8 Gy) Eine prospektive Studie. *Strahlentherapie und Onkologie* **175**, 500-508 (1999).
190. Nielsen, O.S., Bentzen, S.M., Sandberg, E., Gadeberg, C.C. & Timothy, A.R. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **47**, 233-240 (1998).
191. Price, P*., et al.* Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol.* **6**, 247-255. (1986).
192. Roos, D.E*., et al.* Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* **75**, 54-63 (2005).
193. Sarkar, S.K., Sarkar, S., Pahari, B. & Majumdar, D. Multiple and single fraction palliative radiotherapy in bone secondaries - A prospective study. **12**, 281-284 (2002).
194. van der Linden, Y.M*., et al.* Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys.* **59**, 528-537. doi: 510.1016/j.ijrobp.2003.1010.1006. (2004).
195. Cole, D.J. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clinical oncology (Royal College of Radiologists (Great Britain))* **1**, 59-62 (1989).
196. Foro, P., Algara, M., Reig, A., Lacruz, M. & Valls, A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. *Oncologia (Spain)* **21**, 55-60 (1998).
197. Meeuse, J.J*., et al.* Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. *Cancer* **116**, 2716-2725 (2010).
198. Özsaran, Z., Yalman, D., Anacak, Y., Esassolak, M. & Haydaroğlu, A. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. **6**, 43-48 (2001).
199. Safwat, E., El-Nahas, T., Metwally, H., Abdelmotgally, R. & Kassem, N. Palliative fractionated radiotherapy for bone metastases clinical and biological assessment of single versus multiple fractions. *J Egypt Natl Canc Inst.* **19**, 21-27. (2007).
200. Steenland, E*., et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol.* **52**, 101-109. (1999).
201. Yoon, F. & Morton, G.C. Single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients: comparative effectiveness. *Cancer Manag Res* **6**, 451-457 (2014).
202. Storto, G*., et al.* Impact of (1)(8)F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP. *Nucl Med Biol* **40**, 518-523 (2013).
203. Parker, C*., et al.* Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* **369**, 213-223 (2013).
204. Moher, D*., et al.* CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *Journal of clinical epidemiology* **63**, e1-37 (2010).

205. Knaul, F.M.*, et al.* Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the Lancet Commission report. *Lancet* **391**, 1391-1454 (2018).