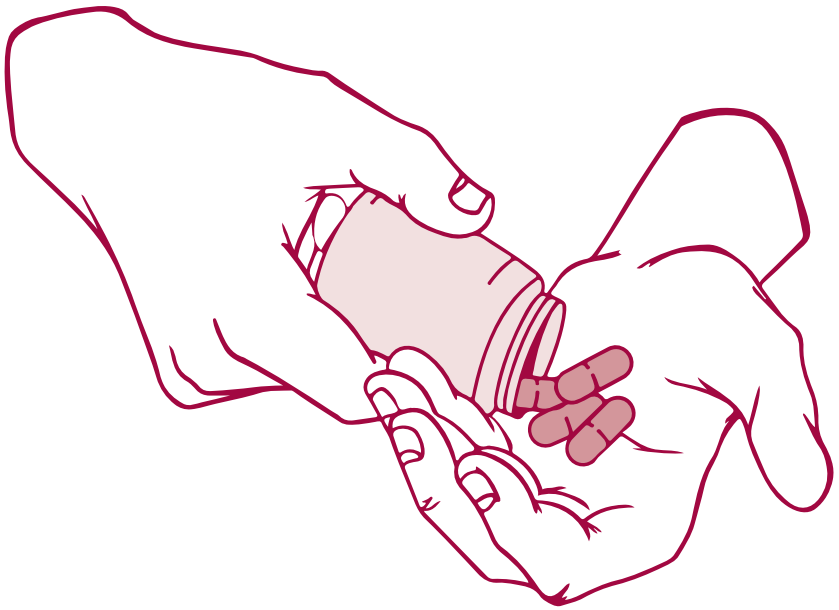
World Health Organization

WHO GUIDELINES FOR THE PHARMACOLOGICAL AND RADIOTHERAPEUTIC MANAGEMENT OF **CANCER PAIN** IN ADULTS AND ADOLESCENTS



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World Health Organization

WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents

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Responsible technical officer: Dr Cherian Varghese

WHO Steering Group members: Marie-Charlotte Bouesseau, Nicolas Clark, Andre Ilbawi, Taskeen Khan, Nicola Magrini and Slim Slama.

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[1] Jim Cleary, representing the University of Wisconsin-Madison Pain and Policies Studies Group was an observer at the first scoping meeting. He was then appointed to the GDG as a member.

[2] Eric Krakauer first joined the guideline development process as a member of the WHO Steering Committee, and following his departure from WHO joined the GDG as a member.

Systematic Review team members: Ethan M Balk (Lead), Gaelen P Adam, Mengyang Di, Hannah J Kimmel, Matthew Olean, Jessica K Roydhouse, Bryant Smith, Andrew R Zullo.

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ABBREVIATIONS AND ACRONYMS

AFR	African Region
AMR	Region of the Americas
BPI	Brief Pain Inventory
CND	Commission on Narcotic Drugs
CPOT	Critical Pain Observation Tool
CR	controlled release
DOI	Declaration of Interests
ECG	electrocardiograph
EMR	Eastern Mediterranean Region
ER	extended-release
ERG	External Review Group
g	gram
GDG	Guideline Development Group
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
h/hr	hour(s)
HR	hazard ratio
INCB	International Narcotics Control Board
INN	Iinternational Nonproprietary Name
IPOS	Integrated Palliative care Outcome Scale
kg	kilogram
L	litre
mcg	microgram
mg	milligram
min	minute(s)
mL	millilitre
NCD	noncommunicable disease
NGO	nongovernmental organization
NMA	network meta-analysis
NSAID	non-steroidal anti-inflammatory drug
NSAIM	non-steroidal anti-inflammatory medicine
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PAINAID	Pain Assessment in Advanced Dementia
PICO	population, intervention, comparator and outcome
PO	by mouth
PR	per rectum
p.r.n.	as needed
q1h	every hour
q4h	every 4 hours
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
RCT	randomized controlled trial
RR	relative risk
SC	subcutaneous
SEAR	South-East Asia Region
SRE	skeletal-related event
TD	transdermal
WHO	World Health Organization
WPR	Western Pacific Region

EXECUTIVE SUMMARY

INTRODUCTION

Cancers are among the leading causes of morbidity and mortality worldwide, responsible for 18.1 million new cases and 9.6 million deaths in 2018, 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 radiotherapeutic management of cancer pain in adults and adolescents* are intended to provide evidence-based guidance to health-care providers on appropriate approaches to initiating and managing cancer pain in adolescents and adults, including older persons. 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

The aims of these guidelines are:

To provide management guidance to health-care 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.

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 radiotherapeutic 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 in this document are organized into three focal areas:

- *Analgesia of cancer pain:* This addresses the choice of analgesic medicine when initiating pain relief and the choice of opioid for maintenance of pain relief, including optimization of rescue medication, route of administration, and opioid rotation and cessation.
- *Adjuvant medicines for cancer pain:* This includes the use of steroids, antidepressants and anticonvulsants as adjuvant medicines.
- *Management of pain related to bone metastases:* This incorporates the use of bisphosphonates and radiotherapy to manage bone metastases.

Following publication of the guidelines, a series of subsidiary products will be developed that will address service delivery aspects of implementation, including World Health Organization (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 Interests (DOI) 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. 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, and 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 considered the relevance of the recommendations for patients with cancer pain, taking account of the balance of benefit and harm of each intervention, the values and preferences of patients, costs and resource use, and other relevant practical issues for health-care 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 which includes comprehensive pain assessment prior to initiating pain relief and ongoing monitoring of pain with adjustments made to dosage and choice of medicine as necessary.

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 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.
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 who 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, among 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 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 antidepressants, anticonvulsants, opioid rotation and clinical regimens currently in established practice, but for which evidence of efficacy for cancer pain is lacking.

1. INTRODUCTION

Cancers are among the leading causes of morbidity and mortality worldwide, responsible for 18.1 million new cases and 9.6 million deaths in 2018 (*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 is 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, 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 those 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.

Patients with cancer may require pain relief at all stages of their disease, and not only at the 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*). As a result of early diagnosis and improved cancer treatment, cancer patients are living longer. Nevertheless, in many settings, patients often present with cancer that is 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 radiotherapeutic, 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 (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 for 90 days (5). Thus, cancer pain is a major cause of unnecessary suffering.

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

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 that "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 Care (*8*).

Despite being an issue of human rights and states' legal obligations, many people do not receive the pain relief they need. In 2006, it was estimated that 5.5 billion people (83% of the world's population) lived 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 World Health Organization (WHO) *Model list of essential medicines* as well as on the list of basic essential noncommunicable 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 are 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 nonpatient 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*), *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 why an update is required namely:

- The 1986 and 1996 guidelines were developed on the basis of reports of a WHO expert committee. Current WHO guidelines are evidence-based using standardized, 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*). The three-step ladder was proposed in 1986 on the basis of the premise that doctors and health-care professionals should learn how to use a few drugs well. There are now new pain assessments, interventions and new delivery methods that were unavailable in 1996 (*21*,*22*,*23*), and new tools have been developed for pain assessment (**Annex 1**).
- There is also a need to provide guidance that 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.

2. OBJECTIVES AND TARGET AUDIENCE OF THESE GUIDELINES

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

1. To provide management guidance to health-care 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.

These guidelines constitute a part of WHO's efforts to promote training, improved knowledge and confidence about appropriate pain relief among health-care providers and public health officials. Through the dissemination and use of the guidelines, 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 the achievement of Universal Health Coverage.

3. SCOPE OF THE GUIDELINES

Pharmacological and radiotherapeutic 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 radiotherapeutic 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 years and over) and adolescents (aged 10–19 years) 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.

4. METHODS USED IN THE GUIDELINES

Full methods of the guideline development process, including the systematic review methods, are provided in **Annex 2**.

In summary, the GDG met on 28–29 July 2016 to outline the scope of the guideline questions and then met again on 20–21 November 2017 to deliberate and determine the recommendations made in response to 13 key clinical questions. The questions included issues such as the optimal choice of medicines for initiating and maintaining cancer pain relief, management of breakthrough pain, use of adjuvant medicines including steroids, anticonvulsants 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 were completed for each question by independent review teams in advance of the meeting and shared with the GDG prior to the meeting. This included a network meta-analysis (NMA) 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). 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 *Handbook for guideline development* was used to provide a rating of the overall quality of evidence arising from each systematic review (categorized as very low, low, moderate or high).

Values and preferences of the intervention were considered from the perspectives of patients. These perspectives were discussed by the GDG members, all of whom had broad professional experience of the field.

When considering the use of resources, the GDG was presented with the pricing of drugs where this was 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 hospitalization and morbidity.

The GDG proffered observations and their own experiences regarding the acceptability of interventions to health-care 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 surveys of patients or health-care providers 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 health-care 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 of each intervention. In the absence of any evidence on a particular review question, the GDG chose to make no recommendation.

For several questions where evidence was scant or lacking, the GDG recognized that established practices exist but did not formulate recommendations for or against the practices. For two such questions, best practice statements were formulated instead in view of the potential benefit and lack of any observed harms from current practices. For those questions where harms or lack of effect were 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 to declare these before the entire GDG. Relevant declared interests of GDG members are reported in **Annex 4**. None of the declared interests were considered by WHO to be conflictual. WHO policies on COI were fully applied throughout.

5. CANCER PAIN MANAGEMENT – GUIDING PRINCIPLES

The GDG and stakeholders who developed the guidelines determined that all recommendations arising from the meeting would be underpinned by the following overarching principles of effective health systems and best clinical practice:

5.1. 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.

5.2. 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 that 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.

5.3. SAFETY OF PATIENTS, CARERS, HEALTH-CARE PROVIDERS, COMMUNITIES AND SOCIETY MUST BE ASSURED

Provision of analgesia for cancer pain management can carry risks to the safety of patients, their families and society more broadly. Consequently, 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 diversion of medicine into society. The safety of health-care providers may also be at risk if they 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 optimized at 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.

5.4. 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 circumstances. Therefore, while pharmacological interventions are the mainstay of cancer pain management, psychosocial care is also an essential component of a comprehensive care plan. Health-care 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. Very anxious or depressed patients should receive appropriate therapy for their psychological needs, which may be pharmacological or otherwise, in addition to an analgesic. If the psychological as well as physiological aspects of pain are not treated, the pain may remain intractable.

5.5. 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 the availability of opioid analgesics.

5.6. 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 increased gradually 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, plus differential diagnosis of the type of pain (e.g. nociceptive somatic pain or nociceptive visceral pain or neuropathic pain), the site of origin of the pain and 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 (**Annex 1**).

With respect to opioids, patients' 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 is always accessible.

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 patients and their families to work from and should include 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.

5.7. 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 the pain. Anti-cancer treatment and pharmacotherapy for cancer pain relief should be given concurrently if the patient is in pain.

6. RECOMMENDATIONS FOR THE PHARMACOLOGICAL AND RADIOTHERAPEUTIC MANAGEMENT OF CANCER PAIN IN ADULTS AND ADOLESCENTS

The following pages present the recommendations and underlying rationale of the expert GDG.

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, while **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
	NSAIDs	Ibuprofen oral tablets and liquid Ketorolac oral tablets and injectable Acetylsalicylic acid oral tablets and rectal suppositories
Opioids	Weak opioids	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, transmucosal lozenge Methadone oral tablet, liquid, injectable

MEDICINE GROUP	MEDICINE CLASS	EXAMPLE MEDICINES
Adjuvants	Steroids	Dexamethasone oral tablet and injectable Methylprednisolone oral tablets and injectable Prednisolone oral tablets
	Antidepressants	Amitriptyline oral tablets Venlafaxine oral tablets
	Anticonvulsants	Carbamazepine oral tablets and injectable
	Bisphosphonates	Zoledronate 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)	LOWER-MIDDLE-INCOME COUNTRY (VIET NAM)	HIGHER-MIDDLE-INCOME COUNTRY (MEXICO)
Morphine 10 mg immediate-release oral	0.13	0.09	0.11
Morphine injectable 10 mg ampule	1.17	0.13	7.73
Dexamethasone injectable 4 mg ampule	0.13	0.04	0.27
Amitriptyline 25 mg tablet	0.01	0.01	0.03
Paracetamol 500 mg tablet	0.01	0.02	>0.01

Source: Knaul et al. 2018 (**5**).

6.1. INITIATION OF PAIN RELIEF

This section presents the recommendations, supporting evidence and rationale for the key clinical questions 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 as to

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 NMA 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, 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' responses to specific analgesic medicines, a range of opioid analgesics should ideally 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, and oxycodone with a single trial comparing weak opioid + NSAID to NSAIDs.

Two of the five trials compared classes of medicine to evaluate relief of pain, providing very low strength of evidence that strong opioids 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 the degree of pain relief, providing very low strength of evidence to favour strong opioids over 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 randomized controlled trials (RCTs) evaluated outcomes other than pain relief among persons 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 (36–47%) (*35*). No studies reported specifically on quality of life. No trial listed or reported on respiratory depression among the study participants.

Rationale

The RCT evidence on the selection of one 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 to 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, they may have concerns about 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 health-care workers and feasibility of provision were likely to be highly variable regionally, although there was agreement that health-care 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. The GDG 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 of evidence.

6.2. MAINTENANCE OF PAIN RELIEF

This section presents 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? 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 a list of detailed questions.

6.2.1. 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, the contraindications and the 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 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** NMA **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 between the interventions (codeine, codeine + ibuprofen, diclofenac, morphine extended release every 12 hours, ketorolac, morphine CR, and morphine immediate-release). Four trials evaluated speed of pain relief, providing low strength of evidence of no significant difference between 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. There was no difference between fentanyl and slow-release morphine for sedation (RR = 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 persons taking tapentadol, but none with morphine slow-release. The studies did not report data to allow for 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 regard 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 was likely to be acceptable to key stakeholders such as clinicians and policy-makers but recognized that, 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 being a concern. However, the GDG 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 recognized that, while increasing the availability of opioids would require an increase in resources including additional training for health-care workers, good pain control leads to an improvement in patient functional status and 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.

6.2.2. 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 4-hourly dose may be considered. In the absence

of evidence, the choice of specific medicine may depend on affordability and ease of administration. As in recommendation 6.2.4, 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 to reduce pain. 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 crossover 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 that were clinically available. The GDG also noted a high degree of uncertainty regarding patient values and preferences, acceptability and feasibility. However, the GDG highlighted that the cost of certain formulations, such as transmucosal fentanyl, was likely to be prohibitively expensive for some low- and middle-income settings, and that 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 decided 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-release or slow-release morphine (see **Section 6.2.4**) and was therefore incorporated into the recommendation and does not appear as a standalone Best Practice statement.

6.2.3. 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.

6.2.4. 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 who 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 having both options available is preferred if resources allow. If a health system must choose between one formulation or the other, 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 according to a fixed schedule.

There is moderate strength of evidence of no difference in pain relief between slow-release and immediate-release morphine. Pooled data from four trials (n = 222) reporting on pain relief showed no difference between Drug A and Drug B (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.

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 showed 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-release 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 the 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 patients in many countries might have access to only 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 health-care 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.

6.2.5. ROUTE OF ADMINISTRATION OF OPIOIDS

Oral administration of opioids is usually 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 because of, for example, dysphagia, bowel obstruction or vomiting (*18*). Consequently, 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 the subcutaneous route is less painful for the patient.

Summary of the evidence

A single small crossover trial compared non-invasive routes versus injected routes for opioids in 20 adults with multiple types of cancer who were selected for the trial because of substantial side-effects related to oral or rectal opioids (*88*). There was very low strength of evidence to suggest a 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 the oral route or the transdermal route, 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 therefore formulated.

6.3. CESSATION OF OPIOID USE

If the cause of cancer pain is effectively addressed by anti-cancer treatment (e.g. 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 questions).

Best Practice statement

If patients have 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 chose 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 persons with opioid dependence undergoing managed withdrawal (*89*,*90*). However, it is not clear whether patients with cancer pain will respond to the evidence-based regimens in the same way as persons 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 individualized opioid cessation plan for patients who no longer require opioid analgesia.

6.4. 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 medicines 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*).

6.4.1. STEROIDS

Steroids are among the most commonly used 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

- In general, steroids should be prescribed for as short a period as possible.
- Optimum dosing of steroids 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 the goals of care, among others.
- When treating cancer pain or complications caused at least in part by 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 (four trials), dexamethasone (two trials) and prednisolone (one trial).

Five trials provided moderate strength of evidence that pain relief was greater in patients taking steroids than in those taking 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 report this adverse event explicitly. 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), while 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.

No trials compared the effects of different steroids against other steroids.

Rationale

Moderate quality of 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 because of their known common side-effects. Older patients are also sometimes reluctant on account of diabetes and other comorbidities. The GDG deemed this 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-effects and adverse events from steroids can be serious, the balance of effects is in favour of their use when indicated; the GDG therefore made a strong recommendation. 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.

6.4.2. ANTIDEPRESSANTS

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

No recommendation

WHO makes no recommendation for or against the use of antidepressants 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 antidepressant use in non-cancer neuropathic syndromes and suggested that practitioners may wish to consider an individual trial of therapy with an antidepressant 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 of evidence that amitriptyline is more effective than placebo in reducing pain in people with cancer-related neuropathic pain; the net difference in Visual Analogue Scale 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 antidepressants to others.

Rationale

While decades of clinical practice have shown antidepressants 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. The GDG therefore opted to make no recommendation because of lack of evidence. The group also noted that some patients might have strong aversions to the use of antidepressants

due to stigma and that possible anticholinergic side-effects, such as dry mouth, constipation or sedation, may be an additional burden.

No eligible trials were found that compared different antidepressants with each other. The GDG could not make a recommendation for one antidepressant in preference to others because of the absence of evidence.

6.4.3. ANTICONVULSANTS

Cancer-related neuropathic pain is common and can be caused either by the disease or by cancer treatment. Anticonvulsants are commonly used as adjuvant 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/anticonvulsants for the treatment of cancer-related neuropathic pain.

Considerations

In the absence of clear evidence in favour of anti-epileptics, 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 anticonvulsants in patients with cancer pain and, wherever possible, should 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 following a revelation of fraud. While gabapentin has been widely prescribed, in 2017 it was rejected for inclusion in the WHO *Model list of essential medicines* 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 are 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.

6.5. MANAGEMENT OF BONE PAIN

Some cancer pains are best treated with a combination of drug and non-drug measures. For instance, radiation therapy, if available, should be considered in patients with metastatic bone pain, or pressure pain from localized cancer (*17*). The *Clinical practice guidelines on management of cancer pain* of the European Society of Medical Oncology recommend radiotherapy (*105*). All patients with pain from bone metastases which is proving difficult to control by pharmacological therapy should be evaluated by a clinical oncologist for consideration of external beam radiotherapy or radioisotope treatment.

6.5.1. BISPHOSPHONATES

Bisphosphonates inhibit osteoclast activity, and their use in cancer patients prevents the increased bone resorption common in metastatic bone disease. Thus they 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 differences 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 equivalent to 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.

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 (three studies), ibandronate (one study) and zolendronate (one 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 SREs (*108*,*109*,*112*,*117–122*,*124*,*127*,*129*,*130*,*132*,*133*, *135*,*137*,*138*,*141–143*,*145–148*). Overall, the trials provided moderate strength of evidence that bisphosphonates reduce the risk of SREs. The six studies that reported hazard ratios for time to first SRE (any) in comparisons of zolendronate (four studies) or ibandronate (two 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 SRE, yielding a summary RR = 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 (*109*,*125*,*132*,*142*). 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 (*148–154*). 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 of age.

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 medicine). 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 of them lung cancer) between ibandronate (5.5 months) and pamidronate (5.2 months) (*151*). 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) (*152*).

Six studies provided very low strength of evidence regarding SREs. Broadly similar percentages of people had any SRE across bisphosphonates (18–26%, with 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 found no significant differences in rates of bone radiotherapy across bisphosphonates and three studies found no significant differences in rates of bone surgery across bisphosphonates.

Three studies reported on rates of hypercalcaemia across bisphosphonates. Two of these found no differences in the incidence of hypercalcaemia between ibandronate (10.7%) and zolendronate (9.3%), and between clodronate (2.9%) and zolendronate (1.4%) respectively. The third trial reported that the hypercalcaemia 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 when 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 the 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 (*155*).

The GDG believed that most patients would prefer bisphosphonates over placebo. However, the GDG recognized that bisphosphonates are also expensive, and 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 (*156–158*). It remains to be seen whether these savings would apply to lower-income settings.

Most of the RCTs were conducted with intermittent intravenous administration. Consideration was given to the issue that administration of the bisphosphonates should be intravenous, but this was not deemed to be a sufficiently significant barrier to administration that the strength of the recommendation should be attenuated. The GDG therefore made a strong recommendation in favour of bisphosphonates.

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

When these considerations are combined, the GDG felt that equity could be affected in either direction. Taking into account the inconclusive evidence and other considerations, the GDG agreed that it could not make a recommendation for one bisphosphonate over another.

6.5.2. 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

Monoclonals 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 (ages 32 to 77 years; mean age 56 years) (*159*). 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 the percentage of people who achieved 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 SREs, 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 specific monoclonal antibodies with other monoclonal antibodies for preventing and treating 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.

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

6.5.3. 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 (*159–168*). All evaluated the monoclonal denosumab and 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 (*163–165*) except for cancer inclusion criteria were separately conducted and reported and were also combined and reported in a summary article (*168*). Patient ages varied widely across studies. Studies were not explicit about what other medicines (including those for pain relief) patients were taking, 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 in 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 SRE (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 hypercalcaemia (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 with bisphosphponates, with a summary RR = 1.40 (95% CI 0.92, 2.13).

Rationale

The systematic review of evidence suggests that monoclonals reduce the risk of SREs and may improve functional outcomes more than bisphosphonates do, but that they 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 do, which patients would prefer, but monoclonals have a significantly higher cost. Osteonecrosis of the jaw (which is 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 SREs 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 those benefits. The GDG agreed it they could not recommend one medicine category over the other on these grounds.

6.5.4. SINGLE-FRACTION 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 (*169*).

Recommendation

In adults (including older persons) and adolescents with pain related to bone metastases, single-dose fractionated 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 metastases; it is not a recommendation concerning preventive radiotherapy.

Considerations

Use of low-fractionated (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-fractionated to high-fractionated radiotherapy (See **Annex 3**, Evidence Profile 6.1) (*170–193*). 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 which used 5 Gy was omitted). High-fractionated radiotherapy ranged from 20 to 30 Gy, mostly given over 5–10 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, with the youngest participant being 16 years of age.

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 nonsignificant differences.

Three studies reported on pain relief speed (i.e. 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 reporting that pain relief was achieved in two weeks in both study arms. Nine studies reported on the 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 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 3–4% of patients had a pathological fracture at the index site (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 recognized 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 fewer trips to receive treatment being an advantage. Similarly, there was likely to be minor variability in acceptability among health-care workers for providing single-dose radiotherapy. Low-fractionated radiotherapy – where a patient receives a larger single dose (e.g. an 8 Gy fraction) in a single clinic visit – is less expensive in terms of both time and money than a longer schedule in which a patient receives smaller individual doses but an overall greater amount of radiotherapy over several visits (e.g. 20–30 Gy given over 5–10 fractions) (*194*). 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-fraction 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 reducing patients' costs, such as those for travel, making the single-dose option the most feasible. For these reasons and the high quality of evidence, the recommendation was strong.

6.5.5. 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 for achieving pain control in adults and adolescents with pain related to bone metastases.

Summary of the evidence

Three RCTs compared radioisotopes to a control arm that did not use radioisotopes (*119*,*195*,*196*). All three trials were conducted in men with prostate cancer. The studies evaluated Strontium-89 (two trials) and Samarium-153 (one trial). Trial participants were mostly older adults with a mean age ranging 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 SREs were less common after radioisotope treatment than placebo (RR = 0.86; 95% CI 0.77, 0.95) and that SREs 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). Another 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 SREs, probably improves quality of life, and may provide greater bone pain relief. However, the GDG decided not to make a recommendation for or against the use of radioisotopes because of their prohibitive cost and the lack of generalizbility of the current evidence, which was drawn only from men with prostate cancer.

7. 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 for pooling results using meta-analysis. It would be helpful for the continuous building of evidence if assessment and measurement of pain are standardized in future cancer pain management trials to allow for statistical data synthesis. For example, a validated scale may be 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 should ensure that methodological quality is not compromised during the conduct of the trial. The CONSORT statement provides a useful template for reporting clinical trials (*197*).

Clinical trial evidence was absent or very limited for the use of several adjuvant therapies, including choice of corticosteroid, and for anticonvulsants and antidepressants, 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, thus 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 and other medicines.

As in many fields, most trials were conducted in high-income settings. Research on cancer pain management should be prioritized 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 (*5*). The latter may be best assessed by using an implementation science approach and a pragmatic trial study design. Studies are also required on the optimal route of administration for opioids and on the cost-effectiveness thereof.

Research on opioids should take account of 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 (e.g. in Europe), opioids are available but have not resulted in an opioid crisis of the scale observed in North America.

The use of cannabinoids was not included as a PICO question in this guidelines process but is currently being widely investigated for both chronic non-cancer and cancer-related pain; trials and syntheses of current data on 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, see **Annex 4**: Background to the development of the guidelines and 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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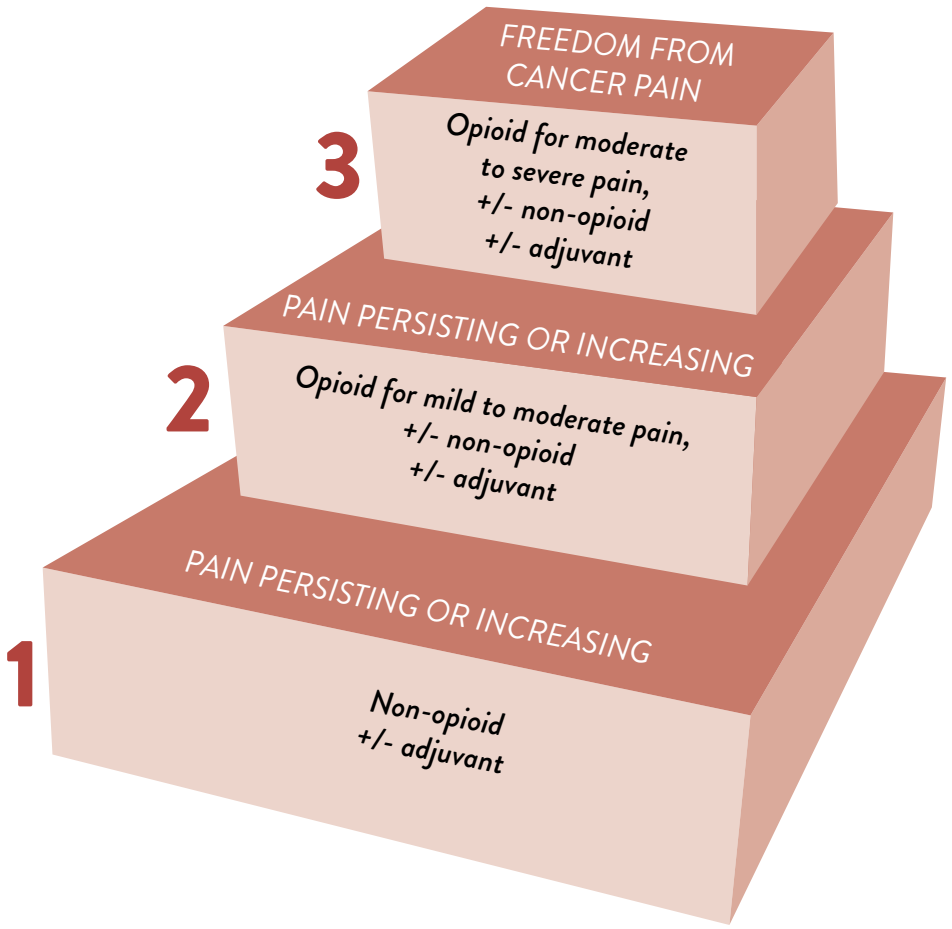
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ANNEXES

ANNEX 1: EVALUATION OF PAIN

Designing optimum analgesia is one of the most fundamental tasks in health care and depends on the evaluation of a patient's pain – including its causes, severity and effects on the patient. However, as a "sensory and emotional experience" that may or may not be associated with tissue damage, evaluation of pain is not always easy (*1*). No single assessment technique is universally applicable. The evaluation must be based in part on clinical judgement regarding factors such as the underlying conditions, haemodynamic stability, acuity of the conditions and the pain, and previous and current treatments. It must also take into consideration psychosocial factors such as

Figure A1.1. The three-step analgesic ladder



the patient's age, culture, religion, mental health, and familial and social situations. Given this complexity, it is not surprising that there is no globally endorsed tool for measuring pain. Nevertheless, pain assessment tools can be an important part of evaluating a patient in pain. Some examples of evidence-based tools for evaluating patients in pain are presented here.

NB: The choice of these examples should not be construed as a clinical recommendation.

A cancer pain management ladder is useful as a teaching tool and as a general guide to pain management based on pain severity (**Figure A1.1**). However, it cannot replace individualized therapeutic planning based on careful assessment of each individual patient's pain. The concept of a ladder easily explains the need for pain assessment and for appropriate management of pain based on a pain severity assessment (*2*).

1. BRIEF PAIN INVENTORY

One of the most commonly used tools for assessing pain in adults and adolescents pain scales is the brief pain inventory or BPI (*3*). The BPI (**Figure A1.2**) concisely registers pain location and treatments and also measures pain intensity and the effect of pain on activities of daily life. The inventory has been validated in many languages and with both malignant and non-malignant pain.

Figure A1.2. Brief pain inventory (see next pages)

Source: Cleeland and Ryan 1994 (*3*).

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

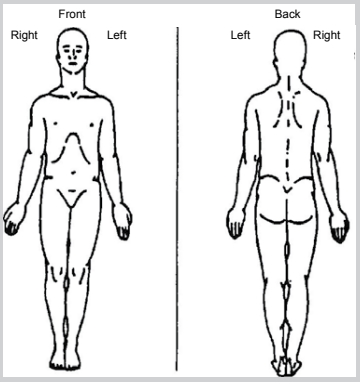
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

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2. CRITICAL CARE PAIN OBSERVATION TOOL

The Critical Care Pain Observation Tool (CPOT, **Figure A1.3**) was developed to enable evidence-based assessment of pain in patients who are critically ill or unable to communicate verbally (*4*).

Figure A1.3. The Critical Care Pain Observation Tool

INDICATOR	DESCRIPTION	SCORE	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movement	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb ou of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
OR	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighting, moaning	Sighting, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

Source: Gélinas et al. 2006 (*4*).

3. PAIN ASSESSMENT IN ADVANCED DEMENTIA

The Pain Assessment in Advanced Dementia tool (PAINAID, **Figure A1.4**) is one of several tools developed to assess pain in patients with advanced dementia (*5*,*6*). Others include Doloplus-2 (*7*) and the Pain Assessment Checklist for Seniors with Limited Ability to Communicate-II or PACSLAC-II (*8*).

Figure A1.4. The Pain Assessment in Advanced Dementia tool

PAIN ASSESSMENT IN ADVANCED DEMENTIA (PAINAID)				
	0	1	2	SCORE
Breathing independant of vocalization	Normal	Occasioinal labored breathing. Short period of hyperventilation	Noisy labored breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low-level speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying	
Facial expression	Smiling, or inexpressive	Sad. Frightened. Frown	Facia grimacing	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch.	Unable to console, distracg or reassure.	
			TOTAL	

Source: Warden et al. 2003 (5). Used with permission.

4. INTEGRATED PALLIATIVE OUTCOMES SCALE

General palliative care assessment tools such as the Integrated Palliative care Outcome Scale (IPOS, **Figure A1.5**) (*9*) include pain evaluation scales. Others include the Memorial Symptom Assessment Scale (*10*,*11*), the Edmonton Symptom Assessment System (*12*), and the MD Anderson Symptom Inventory (*13*).

Figure A1.5. Integrated Palliative care Outcomes Scale

For staff use
Patient number:

IPOS Patient Version

www.pos-pal.org

Name: .....

Date (dd/mm/yyyy): / /

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

Thank you.

Q1. What have been your main problems or concerns over the past 3 days?

1. _____
2. _____
3. _____

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past 3 days.

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

Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past 3 days.

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

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Over the past 3 days:

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

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

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

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

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

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Source: Cicely Saunders Institute. The Palliative Care Outcome Scale (POS) (https://pos-pal.org/maix/). Used with permission.

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ANNEX 2: SYSTEMATIC REVIEW AND GUIDELINE METHODS

1. EVIDENCE RETRIEVAL AND APPRAISAL: METHODS

SEARCH STRATEGY

Literature searches were conducted in PubMed, Embase, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews on 16 February 2017. An additional search was conducted in the Cumulative Index to Nursing and Allied Health Literature on 4 April 2017. The searches yielded 11 196 citations. Additional manual searches for existing systematic reviews were conducted on the Cochrane website and at https://guidelines.gov/.

Independent duplicate screening of citations resulted in preliminary acceptance of 454 primary articles and 41 existing systematic reviews. After full text assessment, 195 randomized controlled trials (RCTs) were considered eligible for one or more of the PICO questions; of these 129 had been included in 19 existing systematic reviews (*1–19*). The original plan was to rely fully on the existing systematic reviews for study descriptions, results data and assessment of study methodological quality (risk of bias). However, accessible data from the existing systematic reviews were generally too incomplete or poorly reported to allow this approach; in addition, the systematic review team found many instances of incorrect data or data that they could not find in the original study articles. Therefore, for the vast majority of primary studies from existing systematic reviews, the review team obtained data from the original publications.

ASSESSMENT OF STUDY QUALITY AND METHODS OF REVIEW SYNTHESIS

The methodological quality of study was assessed with the Cochrane risk of bias tool. However, when existing systematic reviews provided study-level quality ratings, the systematic review team used those, regardless of the quality assessment method used. For the evidence profiles, the team conducted two additional steps to allow determination of overall risk of bias, consistent with GRADE methodology, as follows (*20*):

- First, the overall quality of each RCT was determined.
  - If a study had a high risk of bias due to inadequate randomization or allocation concealment methodology, the study was deemed to have *very serious limitations*.

- If randomization **and** allocation concealment methodologies were low risk of bias (or unclear due to inadequate reporting) but the studies did not mask outcome assessors or they had high attrition rates (or a high percentage of study participants not analysed) or there was evidence of selective outcome reporting or there was an important other potential bias, the study was rated overall as having *serious limitations*.
- However, if the study had two or more of these limitations, it was deemed to have *very serious limitations*.
- Otherwise, studies were rated as having *no serious limitations*.
- Studies could have different overall study quality assessments for different outcomes (e.g. if there was high attrition for only one outcome of interest).

- Second, for each outcome within an evidence profile, the risks of bias of all studies were assessed together.
  - If more than half the studies (or the larger, dominant studies) were deemed to have very serious limitations, then the overall evidence base was also deemed to have *very serious limitations*.
  - If this was not the case, but more than half the studies (or the larger, dominant studies) were deemed to have serious (or very serious) limitations, then the overall evidence base was deemed to have *serious limitations*.
  - Otherwise the evidence base was deemed to have *no serious limitations*.

Study findings were assessed for consistency primarily of direction of effect, with lesser emphasis on magnitude of effect and minimal emphasis on differences in statistical significance. When meta-analysis was conducted, the statistical heterogeneity of treatment effect was assessed with the statistical significance of the heterogeneity and the I-squared statistic. However, if the direction of effect was consistent across studies, the heterogeneity of the actual effect size alone did not yield a determination of *inconsistent*.

Given the strict eligibility criteria, the generalizability of all eligible trials was deemed to be directly applicable to adults (or adolescents) with cancer pain. Studies of non-applicable populations were not included. Consequently, assessment of *indirectness* was based primarily on whether the outcomes being assessed were directly relevant to the outcome of interest. The primary reasons for downgrading based on indirectness related to studies that assessed pain outcomes that were not full (or near-full) pain relief but were only a decrease in pain scores (e.g. by 2 points out of 10). Some that included quality-of-life and functional outcome measures were also downgraded if they were deemed to be inadequate measurement tools. Ideally, these indirect outcomes or measures were not included but, where there was limited direct evidence, the systematic review team included them.

The evidence was downgraded for *imprecision* based mostly on small sample size (for continuous outcomes) with an arbitrary total sample size (across arms and studies) of 300 as a threshold and, separately, wide confidence intervals in relation to the measure (or scale). However, if a small study provided a precise estimate, the evidence was not downgraded.

Other considerations were noted. The main ones were used where there was only a single study evaluating a given outcome for a given question. The accuracy of a single study's estimate of an effect size requires corroboration before it can be considered to be adequate evidence to make a clinical decision with any confidence. If a study is large (i.e. well-powered), rigorously conducted, and the outcome evaluated as a primary outcome, then the study may provide higher strengths of evidence.

Where feasible, the systematic review team conducted meta-analyses of categorical and continuous data when there were at least two trials with the same comparisons. The systematic review team was liberal in what it allowed for meta-analysis, taking account of the nature of the review questions. The review team ignored cancer types or other differences in study populations and differences in follow-up durations. The team combined sets of interventions, such as all bisphosphonates or all opioids; it also ignored differences in doses, routes, strengths and other related factors. For categorical outcomes the review team mostly ignored differences in outcome definitions (such as pain relief being complete ["no pain"] or great [e.g. <3/10 on a visual analogue scale]). For categorical outcomes, the team calculated or meta-analysed the risk ratio (RR). The direction of the RR was determined by the outcome being assessed (i.e. for "good" outcomes – e.g. pain relief – higher RR favours the intervention over control; for "bad" outcomes – e.g. skeletal-related events (SREs) – lower RR favours the intervention). Absolute differences were based on meta-analysed risk ratios and meta-analysed control rates.

For continuous measures of pain, quality of life and functional outcomes, the systematic review team first converted the reported measures to uniform scales of 0 to 100. Following standard convention, for pain control 100 = worst pain, and for quality of life and functional outcomes 100 = best status. When necessary, reported scales were reversed to ensure uniform directionality. Other continuous outcomes (e.g. time) were meta-analysed only if comparable units could be used across studies (e.g. studies reporting pain relief in hours were not meta-analysed with studies reporting pain relief in days).

Methods for the network meta-analyses for certain systematic review questions are discussed in **Annex 7**.

2. EVIDENCE TO RECOMMENDATIONS: METHODS

GROUP PROCESSES USED FOR CONSENSUS AND DISAGREEMENT RESOLUTION

At the scoping meeting, the Guideline Development Group (GDG) agreed that Nandi Siegfried would be co-chair for the development of this guideline, and that Eduardo Bruera would be the other co-chair. The GDG convened to determine the direction, strength and wording of the final recommendations. These were established by consensus. Consensus was defined as a position indicated in the group discussion that was summarized for clarification by a chair; if the co-chairs' clarification was not reopened for discussion by a member of the GDG, this was considered unanimous consensus. In cases where unanimity could not be reached, a majority (>50%) vote by raising of hands (of GDG members only and excluding observers, World Health Organization (WHO) staff and other non-GDG parties) determined the final GDG decision. The GDG were offered the possibility for minority notes to be taken and reflected in the discussion of the recommendation in the final guideline, but all decisions found adequate consensus to render this offer unnecessary.

ASSESSMENT OF THE DIRECTION AND QUALITY OF EVIDENCE

The GDG was provided with the full results of the systematic reviews in reports prior to the meeting and the results and the accompanying GRADE assessment of the quality of the evidence was presented at the meeting. The GDG discussed the results and agreed on an overall quality of evidence for each intervention using the following definitions of level of evidence quality in accordance with the GRADE methodology:

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

METHODS FOR ASSESSMENT OF VALUES AND PREFERENCES, ACCEPTABILITY, FEASIBILITY AND EQUITY

Values and preferences were considered from the perspectives of patients, clinicians and policy-makers. These perspectives were outlined and discussed by the GDG members who represented all relevant stakeholder groups in addition to having broad professional experience of the field.

The GDG members offered observations from their own experience regarding the acceptability of interventions to health-care workers and the feasibility of implementing recommended interventions, especially in regions where resources are scarce or absent. Similarly, the effect of provision of an intervention on equity was carefully considered in the GDG discussions.

No formal patient or health-care provider surveys were conducted.

HOW RESOURCES WERE CONSIDERED

Considerations of resource use relied on the *International drug price indicator guide* (*21*), a recent peer-reviewed medication pricing publication (*22*). If prices could not be found in this source, other medication pricing data websites (goodrx.com (*23*), drugs.com (*24*) or pharmacychecker.com (*25*)) were used. GDG members also brought their knowledge of medication prices around the world to these discussions. No formal cost-effectiveness studies were conducted.

DISCUSSION OF RECOMMENDATION STRENGTH AND EVIDENCE QUALITY

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 health-care system, the potential impact on equity and the resource implications, the GDG decided on the direction of the recommendation (either in favour of 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.

Table A2.1 indicates the implications of strong and conditional recommendations.

Table A2.1. Implications of strong and conditional recommendations

IMPLICATIONS	STRONG RECOMMENDATION "WE RECOMMEND… "	CONDITIONAL RECOMMENDATION "WE SUGGEST… "
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

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ANNEX 3: SYSTEMATIC REVIEW EVIDENCE PROFILES AND EVIDENCE-TO-DECISION TABLES

Available online at:
https://www.who.int/ncds/management/palliative-care/Cancer-pain-guidelines-Annex-3.pdf

ANNEX 4: BACKGROUND TO THE DEVELOPMENT OF THE GUIDELINES AND DETAILS OF PERSONNEL

PICO QUESTIONS ANSWERED BY SYSTEMATIC REVIEW

Key Question 1: Choice of pharmacotherapy for analgesia

1.1. In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between NSAIDs, paracetamol (acetaminophen) and opioids at the stage of initiation of pain management in order to achieve rapid, effective and safe pain control?

1.2. In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between opioids for maintenance of therapy in order to achieve rapid, effective and safe pain control?

1.3. In adults (including older persons) and adolescents with pain related to active cancer receiving first-line treatment with opioids for background pain, what is the most effective opioid treatment for breakthrough pain?

Key Question 2: Opioid rotation/switching

2.1. In adults (including older persons) and adolescents with pain related to active cancer and who are taking a single opioid, what is the evidence for the practice of opioid rotation or opioid switching as compared with continuing use of one opioid in order to maintain effective and safe pain control and minimize adverse effects?

Key Question 3: Opioid formulation and route of administration

3.1. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified-release morphine regularly as compared with immediate-release morphine on a 4-hourly or as-required basis, in order to maintain effective and safe pain control?

3.2. In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of using the subcutaneous, transdermal or transmucosal route as compared with the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. adults, including older persons, and adolescents with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?

Key Question 4: Opioid cessation

4.1. In adults (including older persons) and adolescents with cancer-related pain, what is the evidence for certain dosing regimens or interventions in order to cease opioids effectively and safely?

Key Question 5: Adjuvant treatments

5.1. In adults (including older persons) and adolescents with cancer-related pain, are adjuvant steroids more effective than placebo, no steroids or other steroids to achieve pain control?

5.2. In adults (including older persons) and adolescents with bone metastases, what is the evidence for the use of bisphosphonates or monoclonals compared with each other or no treatment or other bisphosphonates in order to prevent and treat pain

5.3. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of antidepressants compared with placebo, no antidepressant or other antidepressants in order to relieve pain?

5.4. In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second-generation anti-epileptics such as gabapentin or first-generation anti-epileptics such as carbamezapine or sodium valproate compared with placebo, no anti-epileptic or other anti-epileptics in order to achieve rapid, effective and safe pain control?

Key Question 6: Radiotherapy

6.1. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for the use of low-fractionated radiotherapy as compared with high-fractionated radiotherapy or radioisotopes in order to achieve rapid, effective and safe pain control?

6.2. In adults (including older persons) and adolescents with pain related to bone metastases, what is the evidence for radiotherapy or radioisotopes as compared with no radiotherapy or radioisotopes in order to achieve rapid, effective and safe pain control?

PEER REVIEW

The document underwent peer review and comments were incorporated.

REVIEW AND PLAN FOR UPDATING THESE GUIDELINES

Guidelines will be assessed biennially by reconvening available members of the original steering group in order to decide whether there have been developments that warrant an update of the guidelines. The first of these biennial reviews will be held in 2019.

PLANS FOR DISSEMINATION AND IMPACT EVALUATION

The guidelines are available online in the World Health Organization (WHO) Library database and on the WHO webpages for palliative care, cancer and noncommunicable diseases (NCDs).

The guidelines package will be distributed to the following:

- subscribers to WHO publications, to the WHO mailing list for mandatory free distribution (national chief health executives, ministers of health or directors-general of health, depository libraries for WHO publications, WHO representatives/liaison officers, WHO headquarters library, and libraries of WHO regional and other offices), additional non-mandatory free recipients (competent national authorities for drug control treaties, national centres for the WHO International Drug Monitoring Programme, medicines regulatory authorities), scientific journals, international organizations;
- WHO staff in headquarters and elsewhere, relevant nongovernmental organizations (NGOs) in official relations with WHO (including Médecins sans Frontières, International Federation of Pharmaceutical Manufactures & Associations, International Pharmaceutical Association FIP, World Organization of Family Doctors, Union for International Cancer Control, International Association for Hospice and Palliative Care);
- relevant NGOs not in official relations with WHO as well as donors, potential donors, potential publishers of translated versions, and all those who contributed to the documents.

Conference invitations to discuss and present the guidelines will be accepted when possible.

A publication in a peer-reviewed journal articulating novel developments that emerge from the systematic reviews will be considered.

It is intended that the guidelines should be available in all the official languages of WHO, and NGOs in official relations with WHO will be encouraged to support translation of the guidelines through their activity workplans with WHO. Translation into non-United Nations languages and publication in these languages by third parties will be encouraged.

DERIVATIVE PRODUCTS

It is hoped that these guidelines will be the first step in a series of clinical guidelines on symptom management in palliative care. The guidelines will also add to the growing compendium on pain management guidance.

IMPLEMENTATION, ADAPTATION AND EVALUATION

Implementation will be facilitated through WHO regional and country offices. Ongoing cancer control programmes and palliative care programmes will be supported with the new guidelines. The new guidelines will be provided to various palliative care training programmes which will be encouraged to include them in their curricula. The guidelines will be assessed for their implementation following their dissemination. It is believed, however, that the degree to which they are implemented depends more heavily on the regulatory frameworks of each country than it does on the willingness to use the guidelines. One of the primary goals of the guidelines is to create a policy environment that is favourable to the development of balanced national policies for uses of controlled essential medications. Therefore, useful proxies for the impact of the guidelines will be the extent of their dissemination and the degree of interest in them. The number of downloads from the WHO website and the sales of printed copies can be measured and used as a metric of dissemination. The number of translations by third parties is also an indication of the impact that others expect that the guidelines will have.

For local adaptations of the guidelines, WHO encourages potential adapters to contact the relevant WHO focal point for the guidelines to help identify resources that will aid adaptation to their particular locality.

The guide will be evaluated through a user-feedback questionnaire disseminated by the steering group one year after the initial publication of the guidelines.

CONTRIBUTORS TO THIS PUBLICATION

SYSTEMATIC REVIEW TEAM

Ethan M Balk, MD, MPH (Lead)
Gaelen P Adam, MLIS
Mengyang Di, MD, PhD
Hannah J Kimmel, MPH
Matthew Olean, BS
Jessica K Roydhouse, PhD
Bryant Smith, MPH
Andrew R Zullo, PharmD, PhD

The systematic review team was the Brown Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, Rhode Island, United States. The team was led by Ethan Balk. The systematic review team carried out all literature searches, determined the eligibility of existing systematic reviews and primary studies, completed data extraction and risk of bias (quality) assessment, and completed

the summary tables and preliminary evidence profiles. The systematic review team conducted all pairwise meta-analyses.

NETWORK META-ANALYSIS TEAM

Georgia Salanti (Lead)
Orestis Efthimiou
Adriani Nikolakopoulou

The network meta-analysis team came from the Institute of Social and Preventive Medicine, University of Bern, Switzerland. The team is led by Dr Georgia Salanti, a leading expert in the use of GRADE in network meta-analyses. The network meta-analysis team worked with the systematic review team on review questions 1.1–1.3 to ensure that the data collected were suitable for use in a network meta-analysis. The network meta-analysis team developed the network meta-analysis (NMA) outputs that helped inform Guideline Development Group (GDG) recommendations in accordance with GRADE methodology.

GRADE METHODOLOGIST

The guideline methodologist for these guidelines is Dr Nandi Siegfried MBChB, MPH (Hons), FCPHM (SA), DPhil (Oxon).

EXTERNAL OBSERVERS

Representatives from the following organizations observed, and were invited to comment on, the scoping of the guidelines in July 2016: International Association for Hospice and Palliative Care, Worldwide Hospice and Palliative Care Alliance, International Association for the Study of Pain, Union for International Cancer Control, Physicians for Responsible Opioid Prescribing, Médecins Sans Frontières, IMAI-IMCI Alliance.

WHO GUIDELINE STEERING GROUP

Dr Cherian Varghese (Responsible Technical Officer)
HQ/NMH/NVI/MND – Management of Noncommunicable Diseases

Dr Andre Ilbawi
HQ/NMH/NVI/MND – Management of Noncommunicable Diseases

Dr Nicola Magrini HQ/HIS/EMP/PAU – Essential Medicines and Health Products; Policy, Access and Use

Dr Marie-Charlotte Bouesseau
HQ/HIS/SDS – Service Delivery and Safety

Dr Nicolas Clark
HQ/NMH/MSD/MSB – Mental Health and Substance Abuse

Dr Slim Slama
EM/RGO/NMH/NCD/NCM – Noncommunicable Disease Management

Mr Lee Sharkey
HQ/NMH/NVI/MND – Consultant, Management of Noncommunicable Diseases

CHARACTERISTICS AND DECLARATIONS OF INTERESTS OF THE GUIDELINE DEVELOPMENT GROUP

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Dr Gauhar Afsan	Aga Khan University Hospital, Karachi, Pakistan	EMR	Female	MBBS, FCPS (Anaesthesiology). Anaesthesiologist; pain management; guideline development	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Dr Zipporah Ali	Executive Director Kenya Hospices and Palliative 9696Care Association (KEHPCA), Nairobi, Kenya	AFR	Female	MD, MPH, Masters in Palliative Care, HonDUniv (Palliative Care) Palliative care specialist; guideline development; pain policy	Board member (trustee) of the International Children's Palliative Care Network (unpaid)	Considered to have no significant conflicts of interest. No conflict management required.
Dr Chioma Asuzu	College of Medicine, University of Ibadan, Ibadan, Nigeria	AFR	Female	BSc Nursing, M Ed Counselling Psychology, PhD (Clinical Psychology), Diploma in Cancer Prevention and Control, Diploma in Molecular Prevention Psycho-oncology; nursing; psychology	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Dr Eduardo Bruera	The University of Texas MD Anderson Cancer Center, Houston, Texas, United States	AMR	Male	MD, FAAHPM Medical oncology; palliative care; pain management	Participated in Institute of Medicine funded project on Care at the End of Life (committee member and author), completed in 2015	Considered to have no significant conflicts of interest. No conflict management required.
Dr Jim Cleary	University of Wisconsin Carbone Cancer Center; Pain and Policy Studies Group, Wisconsin, United States	AMR	Male	MBBS, FAChPM Palliative care; pain management; pain policy	No conflicts declared	

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Dr Malcolm Dobbin	Senior Medical Advisor, Victorian Department of Health, Melbourne, Australia	WPR	Male	PhD, MBBS, Dip Obstetrics RANZCOG, MPH, FAFPHM Public health; toxicology; misuse of pharmaceuticals, health policy	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Dr Kathleen Foley	Attending neurologist emeritus at Memorial Sloan-Kettering Cancer Center, Pain and Palliative Care Service, New York, United States	AMR	Female	BS (Biology), MD Palliative care; cancer pain; pain management; neurology	Former director and medical director of Open Society Foundations' (1995–2015) efforts to advance access to palliative care	Considered to have no significant conflicts of interest. No conflict management required.
Ms Harmala Gupta	CanSupport, New Delhi, India	SEAR	Female	BA (Hons) Economics, MA International Politics, MPhil Chinese Studies. Palliative care policy; Patient experience; cancer survivorship	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Dr Eric Krakauer	Harvard Medical School Center for Palliative Care, Boston, Massachusetts, United States	AMR	Male	MD, PhD Palliative care; pain policy	No conflicts declared	
Dr Philip Larkin	School of Nursing Midwifery and Health Systems, Health Sciences Centre, University College Dublin, Dublin, Ireland	EUR	Male	PhD (Palliative care), MSc (Palliative Care Education), BSc (Hons) (Community Health), Registered Nurse, RSCN, RHV, District Nurse, Registered Nurse Tutor Palliative care nursing	Elected president of the European Association of Palliative Care (2015–2019) (unpaid)	Considered to have no significant conflicts of interest. No conflict management required.
Mr Diederik Lohman	Human Rights Watch, United States	AMR	Male	BA (propedeuse) Russian Language and Culture, MA Russian Studies and Law Human rights, pain policy	Received US$ 266 000 of institutional research funding from Atlantic Philanthropies to conduct qualitative and policy research and advocacy related to palliative care (2015–2016)	Considered to have no significant conflicts of interest. No conflict management required.

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Dr Sebastian Moine	General practitioner, Amiens University Hospital, Paris, France	EUR	Male	BSc, MA Biological and medical sciences, MD, Diploma in Palliative Care, MSc in Ethics of health practices, health care, and hospital institutions, MSc in Ethics, chronic disease, end-of-life and palliative care, Diploma in Active learning and simulation in health care Primary palliative care; General practice	Received €385 750 institutional research funding from French Ministry of Health to develop and assess a complex intervention in primary palliative care (2015–2019)	Considered to have no significant conflicts of interest. No conflict management required
Dr Hibah Osman	Balsam-Lebanese Center for Palliative Care, Beirut,Lebanon	EMR	Female	MD, Family Medicine & Hospice and Palliative Medicine Executive and Medical Director and Founder, Balsam Clinical Associate at the American University of Beirut Medical Center	No conflicts declared	
Dr Lukas Radbruch	Director of the Department of Palliative Medicine, University Hospital Bonn, Bonn, Germany	EUR	Male	MD, speciality certificate (anaesthesiology) Palliative care; pain management; pain policy	President of the German Association for Palliative Medicine since 2014 and Chairman of the Board of Directors of the International Association for Hospice and Palliative Care (IAHPC)	Considered to have no significant conflicts of interest. No conflict management required
Dr MR Rajagopal	Trivandrum Institute of Palliative Sciences, Trivandrum, Kerala, India	SEAR	Male	BSc (Zoology), MBBS, MD (Anaesthesiology), MNAMS (Anaesthesiology) Anaesthesiology; palliative care; pain policy	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Dr Paul Sebastian	Director of the Regional Cancer Centre, Trivandrum, Kerala, India	SEAR	Male	MBBS, MS (General surgery) Surgical oncology	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required
Dr Nandi Siegfried	Co-Director of the South African Cochrane Centre at the Medical Research Council (MRC), Cape Town, South Africa	AFR	Female	MBChB, MPH (Hons), FCPHM (SA), DPhil (Oxon) Guideline methodology	Has received approximately US$ 50 000 from consultancy work with WHO over last four years (ongoing)	Considered to have no significant conflicts of interest. No conflict management required
Dr Catherine Stannard	Pain Clinic, Gloucester House, Southmead Hospital, Bristol, United Kingdom	EUR	Female	MB ChB, FRCA, FFPMRCA Pain management; guideline development	From 2014–2016, chaired clinical and policy group (unpaid) on behalf of public bodies in the UK, to develop resource to support prescribers of opioids in the UK, and risks of misuse of gabapentin and pregabalin	Considered to have no significant conflicts of interest. No conflict management required
Dr Jane Turner	University of Queensland, Brisbane, Queensland, Australia	WPR	Female	MBBS, PhD, FRANZCP Psychiatry; psycho-oncology; guideline development	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required
Dr Verna Vanderpuye	Department of Radiotherapy, Korle – Bu Teaching Hospital, Korle – Bu, Ghana	AFR	Female	MB ChB FWACS, FGCP Radiation oncology; medical oncology	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required
Ms Verna Walker-Edwards	Ministry of Health, Jamaica	AMR	Female	BSc and Diploma in pharmacy, Diploma in Management Studies, MSc in Health Administration Pharmacist; pain policy	Recipient of International Pain Policy Fellowship from Pain Policy Studies Group, University of Wisconsin (2008–2012)	Considered to have no significant conflicts of interest. No conflict management required

Regional representation: AFR (4); AMR (6); EMR (2); EUR (4); SEAR (3); WPR (2). Gender balance: Female (11); Male (10).
Note: AFR = African Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South-East Asia Region; WPR = Western Pacific Region.

CHARACTERISTICS AND DECLARATIONS OF INTERESTS OF THE EXTERNAL REVIEW GROUP

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Samy Alsirafy	Palliative Medicine Unit, Kasr Al-Ainy Centre of Clinical Oncology & Nuclear Medicine (NEMROCK), Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt	EMR	Male	MBBCh, MSc in radiotherapy, MD in radiotherapy, Diploma of the American Board of Hospice and Palliative Medicine (DABHPM), Diploma in Palliative Medicine	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Roger Chou	Oregon Health & Science University, Portland, Oregon, United States	AMR	Male	MD, Fellow of the American College of Physicians	Research support for employer (CDC) (Amount assumed significant in size) – Received research funding to conduct systematic reviews on opioids for chronic (non-cancer) pain	Considered to have no significant conflicts of interest. No conflict management required.
Michel Daher		EMR	Male	MD, Fellow of the American College of Surgeons (FACS), Fellow of the European Board of Surgery (FEBS)	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Beena Devi	Saint Georges Hospital University Medical Center, Beirut, Lebanon	WPR	Female	MBBS, MD in Radiotherapy, Diploma of Medicine (Palliative care), M Med (Palliative care)	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Julia Downing		AFR	Female	BN, Diploma (Cancer Nursing) MS (Clinical oncology), PhD (Palliative Care Education)	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Andy Gray	Sarawack General Hospital, Jalan Hospital, Sarawak, Malaysia	AFR	Male	B Pharm, MSc (Pharm), FPS, FFIP	Member of the South African Medicines Control Council (since 2015), and two of its expert committees: Legal Committee (since 2016) and Names and Scheduling Expert Committee (since 2000) Member of the South African National Essential Medicines List Committee (since 2014) Member of the WHO Expert Panel on Drug Policies and Management (since 2007), and a member of the WHO Expert Committee on the Selection and Use of Essential Medicines at various times (most recently, 2011, 2013) Past member of the WHO Guidelines Review Committee (completed term in 2013)	Considered to have no significant conflicts of interest. No conflict management required.
Parmanand Jain	Makerere University, Kampala, Uganda	AMR	Female	BS (Biology), MD Palliative care; cancer pain; pain management; neurology	Committee (since 2016) and Names and Scheduling Expert Committee (since 2000)	Considered to have no significant conflicts of interest. No conflict management required.
Brian Kelly	University of KwaZulu-Natal, Durban, South Africa	SEAR	Female	BA (Hons) Economics, MA International Politics, MPhil Chinese Studies Palliative care policy; Patient experience; cancer survivorship	Member of the South African National Essential Medicines List Committee (since 2014)	Considered to have no significant conflicts of interest. No conflict management required.
Emmanuel Luyirika	African Palliative Care Association, PO BOX 72518 850 Dr Gibbons Road, Kampala, Uganda	AFR	Male	MB, ChB, Master of Family Medicine (M FAM MED), Post graduate Honours Degree in Public Administration ((BPA) Hons), MPA	Employee of African Palliative Care Association	Considered to have no significant conflicts of interest. No conflict management required.

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Geoff Mitchell	School of Medicine, University of Queensland, Brisbane, Australia	WPR	Male	PhD, MBBS, FRACGP, FAChPM	Site investigator for novel analgesic. Current. Funds delivered on recruitment – Southern Star Research, Australia	Considered to have no significant conflicts of interest. No conflict management required.
Anil Paleri	Institute of Palliative Medicine, Medical College PO, Kozhikode, Kerala, India	SEAR	Male	MBBS, Postgraduate Diploma (Anaesthesiology), Postgraduate Diploma of Medicine (Palliative Care), Diploma in Palliative Medicine	No conflicts declared	Considered to have no significant conflicts of interest. No conflict management required.
Tania Pastrana	Latin American Association for Palliative Care and Department of Palliative Medicine, University Hospital TWTH, Germany	AMR	Female	MD, Doctorate in Medical Anthropology	President of the Latin American Association for Palliative Care (ALCP) Works to increase access to palliative care globally Has received money from IAHPC (in official relations with WHO) to volunteer at WHO headquarters	Considered to have no significant conflicts of interest. No conflict management required.

	Organizational affiliation	WHO region	Gender	Expertise	Disclosure of interest	Conflict of interest and management plan
Nguyen Thi Phuong Cham	Centre for Community Health Development, Viet Nam	WPR	Female	Senior Pharmaceutical Expert (retired), Consultant Vietnam Administration Medical Services (Ministry of Health)	Consulting, including, service a technical or other advisor: 1. For Palliative Care – Training on Pain Policy for physicans and heat of hospital and heath service in Vietnam (Pain and Policy Studies Group – "Assumed to be significant" – April 2012); 2. For Rational Use of Drugs - Training courses on activities of Drug Therapy Committee and pharnmacology (Ministry of Health – Volunteer – April 2012 to 2017) – Assessment on quality of diagnosis and prescription and DTC in the project supported hospitals (GIZ – "assumed to be significant" – August 2016)	Considered to have no significant conflicts of interest. No conflict management required.
Maggie Watson	Pastoral and Psychological Care, Royal Marsden NHS Trust, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom	EUR	Female	BSc (Hons) Sociology, Ph.D. Psychology, Diploma in Clinical Psychology, AFBPS	President of the German Association for Palliative Medicine since 2014 and Chairman of the Board of Directors of the International Association for Hospice and Palliative Care (IAHPC)	Considered to have no significant conflicts of interest. No conflict management required.

Regional representation: AFR (3); AMR (3); EMR (2); EUR (1); SEAR (2); WPR (3). Gender balance: Female (5); Male (7).
Note: AFR = African Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = South-East Asia Region; WPR = Western Pacific Region

HOW COMPETING INTERESTS WERE MANAGED

Each member of the GDG was asked to complete a WHO Declaration of Interests (DOI) form before the initial GDG scoping meeting and guideline formulation meetings. All conflicts of interest reported were reviewed by the guidelines coordinator and the responsible technical officer. In five cases of potentially significant conflicts of interest (financial or nonfinancial), advice was sought from the Secretariat of the Guidelines Review Committee and WHO's Department of Compliance, Risk Management and Ethics (CRE) as to whether the conflicts warranted one of several actions: exclusion from the GDG; exclusion from one or more topic areas; inclusion in all of evidence review sessions, but exclusion from final voting on recommendations; no action required. The Director of the Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVI) made the final decision to exclude the five candidates with potentially significant conflicts of interests from the GDG, based on advice from the Steering Group and CRE colleagues. GDG members were instructed to update their DOIs throughout the process with any potentially relevant change by notifying the responsible technical officer and the guidelines coordinator.

Owners, co-owners and members of advisory boards of pharmaceutical companies were excluded from the External Review Group (ERG) and GDG membership and from participation in other parts of the development process. Board memberships and directorships of professional bodies were evaluated for their potential to be conflicts of interest, as were the funding sources of the bodies. All GDG members were asked to share their *curricula vitae*, and a brief biography of all potential members was published publicly on the WHO website from June to September 2016. There was a standing agenda item on "Conflicts of Interests" at the beginning of all Guideline Development Group meetings where declared conflicts of interest were presented before the entire GDG. Relevant declared conflicts of interest of GDG members were reported in the guidelines publication, as was the strategy employed to manage conflicts of interest during the meeting. WHO policies on conflicts of interest were fully applied throughout.

ANNEX 5: OPIOID ANALGESICS AND INTERNATIONAL CONVENTIONS

Source: Adapted from *Guidelines on the pharmacological treatment of persisting pain in children with medical illness*. WHO 2012 (*1*).

This annex provides an overview of the rules for procurement, distribution and dispensing of opioid medicines and of their status as controlled medicines under the United Nations Single Convention on Narcotic Drugs, 1961. The annex is intended to guide policy-makers, managers, health-care officials and health-care providers to improve the safe accessibility of opioid analgesics for medical needs through policy development and health system planning.

The World Health Organization (WHO) published the policy guidelines *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines to assist countries to optimize access to all controlled medicines and to prevent harm from substance misuse* (*2*). WHO encourages governments, health-care providers and civil society to strive towards a balance in national opioid policies so that access to opioids for rational medical uses is maximized and hazardous or harmful uses are minimized.

UNITED NATIONS DRUG CONVENTIONS AND THEIR GOVERNANCE SYSTEM

There are three international drug control treaties: the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol (*3*); the United Nations Convention on Psychotropic Substances, 1971 (*4*); and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988 (*5*). These conventions represent a global effort to prevent drug abuse, while enabling access to these substances as medicines for the relief of pain and suffering. By signing these treaties, countries have made a commitment to implement a number of drug control measures in their territories without unduly restricting access to medicines.

The Commission on Narcotic Drugs (CND), which represents the States Parties to these international drug conventions, has the authority to decide, upon a recommendation from WHO, whether a substance should be scheduled as a narcotic drug or a psychotropic substance. The process for developing the recommendations for scheduling drugs under these two conventions is described in the *Guidance for the WHO review of psychoactive substances for international control* (*6*). The International Narcotics Control Board (INCB) is charged with monitoring governments' compliance with the above international treaties and ensuring, on the one hand, that controlled

substances are available for medical and scientific use and, on the other hand, that the drugs are not diverted from licit sources to illicit markets.

THE SINGLE CONVENTION ON NARCOTIC DRUGS AND OPIOID ANALGESICS

The Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol (*3*) is the principal international treaty regulating the control of opioids. It seeks to limit the production, manufacture, exportation, importation, distribution, trade, use and possession of narcotic drugs exclusively to medical and scientific purposes. The Single Convention distinguishes four types of classification: Schedule I, Schedule II, Schedule III and Schedule IV. Each schedule refers to a number of control measures to be applied according to the gravity of drug abuse and dependence produced by the listed substances. Morphine and the other strong opioids such as fentanyl, hydromorphone, oxycodone, methadone and others, are listed under Schedule I. In order to comply with the Single Convention, countries should take the following measures for narcotic substances listed under Schedule I:

- estimate the annual medical and scientific requirements and submit their estimates to the INCB for confirmation;
- limit the total quantities manufactured and imported to the estimates, taking into account the quantity exported;
- ensure they remain in the hands of licensed parties for trade and distribution within the country;
- require a medical prescription to be dispensed for their use;
- report to the INCB on the amount imported, exported, manufactured, consumed and on the stocks held;
- maintain a system of inspection of manufacturers, exporters, importers and wholesale and retail distributors of narcotic drugs, and of medical and scientific institutions that use such substances, and ensure that premises, stocks and records are inspected; and
- take steps to prevent the diversion and abuse of these substances.

The Single Convention states in its preamble: “recognizing that 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”. This puts an obligation on the countries that are Parties to the international conventions to ensure the medical availability of the controlled substances.

DRUG MISUSE VERSUS PATIENT NEED

The Single Convention recognizes that governments have the right to impose further restrictions, if they consider it necessary, to prevent diversion and misuse of opioids. However, this right must be continually balanced against the responsibility to ensure opioid availability for medical purposes.

In deciding the appropriate level of regulation, governments should bear in mind the dual aims of the Single Convention. The INCB has observed that, in some countries, fear of drug misuse has resulted in laws and regulations, or interpretations of laws and regulations, which make it unnecessarily difficult to obtain opioids for medical use:

> … prevention of availability of many opiates for licit use does not necessarily guarantee the prevention of the abuse of illicitly procured opiates. Thus, an overly restrictive approach to the licit availability of opiates may, in the end, merely result in depriving a majority of the population of access to opiate medications for licit purposes (*7*).

In its annual report of 2004, the INCB furthermore acknowledged that there was a huge disparity in countries' access to opioid analgesics for pain relief. It reported that six developed countries accounted for 79% of the global consumption of morphine. Conversely, developing countries, which represent 80% of the world's population, accounted for approximately 6% of the global consumption of morphine (*8*). A study on the adequacy of opioid consumption around the world concluded that 5683 million people live in countries where the consumption level of strong opioid analgesics is below adequate, against 464 million in countries with adequate consumption of strong opioids. An additional 433 million people live in countries for which no data are available (*9*).

Drug control conventions were established to enhance public health, which is affected positively by the availability of controlled medicines for medical treatment and affected negatively by misuse and dependence. Countries should seek the optimum balance in order to attain the best outcomes for public health.

> Governments should examine their drug control legislation and policies for the presence of overly restrictive provisions that affect delivery of appropriate medical care involving controlled medicines. They should also ensure that provisions aim at optimizing health outcomes and take corrective action as needed. Decisions which are ordinarily medical in nature should be taken by health professionals. For doing so, they can use the WHO policy guidelines, specifically *Ensuring balance in national policies on controlled substances* (*2*), especially the country checklist contained in that publication.

COMPETENT NATIONAL AUTHORITIES UNDER THE INTERNATIONAL DRUG CONTROL TREATIES

The national legislation in countries that have ratified the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, designates a competent national authority to liaise with the INCB and the competent authorities of other countries. These competent national authorities also administer national regulations relating to controlled substances for medical use. The office of the competent national authority is usually located in the national medicines regulatory authority and/or in the Ministry of Health. In certain countries, the competent national authority is a separate government agency; in others, it is an office located in another ministry, such as the ministries of justice, police or finance.

The identification of the competent national authority is a necessary step for any manager and officer involved in the planning of the procurement and supply of opioid analgesics. A list of country competent authorities and their contact details is available.[1]

THE CONVENTION'S REQUIREMENTS FOR NATIONAL ESTIMATES OF MEDICAL NEED FOR OPIOIDS

Every year, competent national authorities must prepare estimates for the following calendar year of their requirements for Schedule I narcotic drugs (morphine and other strong opioid analgesics) and Schedule II (*10*). These estimates are submitted to the INCB and set the yearly limits for the amount of strong opioids to be procured for medical use. The estimates must be submitted to the INCB by 30 June, six months in advance of the period to which they apply. The INCB notifies confirmed estimates to the competent national authorities by December of the same year.

Under the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, the quantity of controlled substances manufactured or imported into a country must not exceed the official government estimates. Therefore, the submission of adequate estimates to the INCB is crucial when importing controlled substances, as exporting countries will refuse to export additional narcotic substances to a country that has used up the quantity it is allowed to import for the calendar year.

The responsibility for determining the amount of opioids needed to meet medical and scientific requirements in a country rests entirely with the government, although the INCB may examine the estimates and request additional information and clarification. If countries fail to establish estimates of annual narcotics requirements, the INCB determines them on their behalf. In such cases, the INCB informs the competent national authority of the country concerned of its estimates and requests the authority to review them.

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[1] See: http://www.painpolicy.wisc.edu/countryprofiles, accessed 4 October 2018).

THE IMPORTANCE OF RELIABLE ESTIMATES

WHO and the INCB are working on a joint guide for estimating requirements for substances under international control. This is a particularly important step in the supply cycle of opioid analgesics as it ensures the uninterrupted supply of these essential medicines. Countries introducing or enlarging the coverage of pain relief services will need to forecast adequately the quantities of opioid analgesics that will be increasingly supplied in the health system.

If an annual estimate proves to be inadequate, the competent national authority can submit supplementary estimates to the INCB at any time during the course of the year. However, the competent national authority will be requested to provide an explanation of the circumstances necessitating additional drug quantities. As far as possible, such supplementary estimates should be used only in the case of unforeseen circumstances and for the introduction of new treatments (*11*).

> The market availability of controlled substances is confined to the estimates submitted to the INCB. Hence, it is crucial for managers and other parties concerned with the procurement of strong opioids to be aware of national estimates for the relevant drugs. The Board publishes changes in the estimates received from governments on a monthly basis on the Internet (www.incb.org), or on a quarterly basis in the form of a hard copy technical report sent to governments, as a guide to exporting countries.

DOMESTIC MANUFACTURE OF STRONG OPIOID ANALGESICS

After a country has received confirmation of its estimates from the INCB, it may start procedures for manufacturing or importing of opioid analgesics under Schedule I. The Single Convention requires governments to license individuals and enterprises involved in the manufacture of opioid medicines. In order to prevent the diversion of these strong opioids to illicit markets, manufacturers must make resources available for recordkeeping and security procedures, as well as for the provision of secure facilities from the moment the raw materials are acquired until the finished products are distributed.

In addition, governments should assure the quality of the manufactured medicines, such as by enforcing Good Manufacturing Practices and the requirement of a market authorization by the national medicines regulatory authority.

Special reporting to INCB is additionally requested regarding:

- the quantities of opioid medicines to be used in the manufacturing of other medicines;

- the number of industrial establishments that will manufacture opioid medicines; and
- the quantities of opioid medicines to be manufactured by each establishment.

THE IMPORT/EXPORT SYSTEM FOR STRONG OPIOIDS

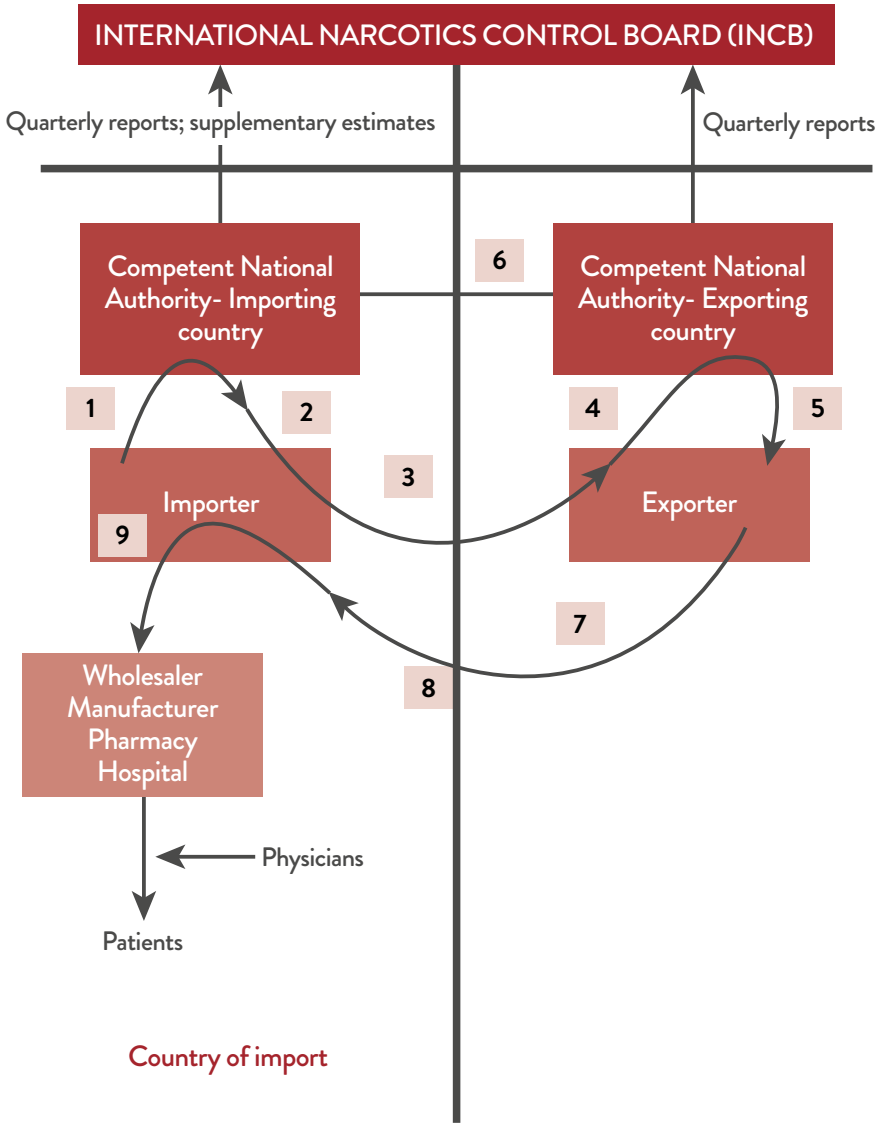
The principles governing the procurement and supply of strong opioid medicines are similar to those for other pharmaceutical products but require additional steps, as mandated by the Single Convention and national legislation.

Generally, each country has its own importation procedures, which may require approval from different authorities in the country, such as the Ministry of Health, the national medicines regulatory authority and other entities (e.g. for import duties).

Specifically, the Single Convention requires additional steps and approvals for the importation and exportation of narcotic drugs. These steps, outlined below and in **Figure A5.1**, are broadly applicable across countries, although specific requirements may vary from country to country.

1. The licensed importing entity (e.g. private or public company) applies for an import authorization from the importing country's competent authority. It should be noted that, while the competent authorities in some countries are different from the national medicines regulatory authority, in others they may be one and the same authority.
2. The competent authority considers whether the entity is properly licensed and whether the amount of drug required is within the national estimate. If so, the competent authority issues an original import certificate in the appropriate number of copies. The original and one copy are for the importer, one copy is for the competent authority of the exporting country, and an additional copy is to be kept in the records of the issuing competent authority.
3. The importer sends the original of the import authorization to the company responsible for the export of the substance.
4. The exporter applies to its competent authority for an export authorization and encloses the import authorization with the application.
5. The competent authority in the exporting country checks that an import authorization has been issued and that the exporter is properly licensed. If the application is approved, an export authorization is issued and the original import authorization is returned.
6. The competent authority in the exporting country sends a copy of the export authorization to its counterpart competent authority in the importing country.

Figure A5.1. Steps and approvals for the importation and exportation of narcotic drugs



Source: Reproduced from UNODOC et al. 2018 (*12*).

7. The exporter ships the drugs to the importer, along with the copy of the export authorization and the original import authorization.
8. The shipment must pass two customs inspections: one in the exporting country and one in the importing country.
9. The importer sends the export authorization to its competent authority in the importing country.

REQUIREMENTS FOR IMPORT/EXPORT AUTHORIZATIONS OR CERTIFICATES

Both import and export authorizations should include:

- the international nonproprietary name (INN) of the medicine;
- the quantity of the medicine to be imported or exported;
- the name and address of the importer and exporter; and
- the period of validity of the authorization.

The export authorization should also state the reference number and date of the import authorization, and the name of the issuing authority. The forms for import and export applications may vary from country to country. INCB model forms for these authorizations are available in the *Guidelines for the import and export of drugs and precursor references standards for use by national drug testing laboratories and competent national authorities* (*13*).

Import and export authorizations are normally required for each shipment. One import authorization can allow for more shipments (for which exportation authorization needs to be granted on a single basis).

- The authorization process for the importation and exportation of opioid medicines can be very lengthy and subject to errors. Therefore, the procurement of controlled medicines requires careful planning.
- Managers and officers involved in the procurement of opioid analgesics should use the steps outlined here as a starting point to develop comprehensive plans specific to their countries' situations. Since the importation of controlled medicines involves decision-making and authorizations from several departments/agencies, it is crucial that strong coordination and partnerships are established among all parties.

THE REPORTING SYSTEM FOLLOWING EXPORTATION, IMPORTATION AND CONSUMPTION OF OPIOIDS

The competent national authority in the country must send quarterly reports to the INCB of all imports and exports of opioid analgesics classified under Schedule I. It is also mandatory to make an annual inventory and to report the total amount of opioids manufactured, consumed and held in stock at the central level (e.g. licensed central warehouses, manufacturers' warehouses). The annual inventory does not include medicines stored in retail pharmacies, retail distributors or other health services which, for official purposes, are considered to have been consumed. "Stock" is defined in Article 1 of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol.

DISTRIBUTION OF STRONG OPIOIDS

The Single Convention requires countries to ensure that trade and distribution can be performed only by licensed parties. The competent national authority normally provides trade and distribution licences to private companies, either manufacturers or wholesalers. A manufacturer or wholesaler may distribute the finished products directly to licensed pharmacies or hospitals. Wholesalers must also be licensed by the competent national authority and must comply with rules concerning security and recordkeeping. The Single Convention *neither* requests countries to provide exclusive rights for the storage, distribution and trade of controlled medicines to one single state agency or private company, *nor* suggests that opioids be managed within a special or separate medicine distribution system.

However, some countries have separated the storage and distribution of controlled medicines from the distribution system for other medicines. They have also established additional requirements to those mandated by the Single Convention. These may sometimes have a negative impact on the accessibility to strong opioids and may increase distribution costs.

USUAL REQUIREMENTS FOR PRESCRIBING AND DISPENSING OPIOIDS

The Single Convention requires medical prescriptions to prescribe and dispense controlled medicines to individuals. Legal requirements for prescriptions vary from country to country. However, in accordance with most prescription medicines, a prescription for an opioid analgesic should specify the following:

- the name and business address of the prescribing health professional;
- the name of the patient;
- the date of the prescription;

- the preparation to be dispensed (e.g. morphine tablet);
- the dose to be dispensed in milligrams (words and numbers);
- the frequency of dispensing (e.g. daily, twice daily); and
- the signature of the prescribing doctor or health professional.

Requirements for duplicate prescriptions and special prescription forms increase the administrative burden both for health-care workers and drug control authorities. The problem is compounded if forms are not readily available, or if health professionals need to pay for them. The conventions allow for duplicate prescriptions and special prescription forms if countries consider them necessary or desirable. Governments should ensure that this system does not impede the availability and accessibility of controlled medicines. No limit is set on the quantity of medicines or the length of the treatment inscribed in a prescription.

WORLD HEALTH ASSEMBLY RESOLUTION 67.19 (2014) ON STRENGTHENING OF PALLIATIVE CARE AS A COMPONENT OF COMPREHENSIVE CARE THROUGHOUT THE LIFE COURSE

In 2014, the World Health Assembly (*14*):

- Affirmed that access to palliative care and to essential medicines for medical and scientific purposes, manufactured from controlled substances, including opioid analgesics such as morphine, in line with the three United Nations international drug control conventions, contributes to the realization of the right to the enjoyment of the highest attainable standard of health and well-being;
- Noted that the availability and appropriate use of internationally controlled medicines for medical and scientific purposes, particularly for the relief of pain and suffering, remains insufficient in many countries, and highlighted the need for Member States, with the support of the WHO Secretariat, the United Nations Office on Drugs and Crime and the International Narcotics Control Board (INCB), to ensure that efforts to prevent the diversion of narcotic drugs and psychotropic substances under international control pursuant to the United Nations international drug control conventions do not result in inappropriate regulatory barriers to medical access to such medicines;
- Noted the inclusion of controlled medicines needed for pain control in palliative care settings in the WHO *Model list of essential medicines and the* WHO *Model list of essential medicines for children*; and
- Urged Members States:

- to assess domestic palliative care needs, including pain management medication requirements, and promote collaborative action to ensure adequate supply of essential medicines in palliative care, avoiding shortages;
- to review and, where appropriate, revise national and local legislation and policies for controlled medicines, with reference to WHO policy guidance, on improving access to and rational use of pain management medicines, in line with the United Nations international drug control conventions; and
- to update, as appropriate, national essential medicines lists in the light of the recent addition of sections on pain and palliative care medicines to the WHO *Model list of essential medicines* and the WHO *Model list of essential medicines for children*.

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ANNEX 6: PHARMACOLOGICAL PROFILES AND OPIOID CONVERSION TABLES

I. PHARMACOLOGICAL PROFILES

1. ACETYLSALICYLIC ACID

Suppository: 50–150 mg

Tablet: 100–500 mg

Uses: mild-to-moderate pain including dysmenorrhoea, and headache; pain and inflammation in rheumatic disease and other musculoskeletal disorders, including juvenile arthritis; pyrexia; acute migraine attack; antiplatelet.

Contraindications: hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other non-steroidal anti-inflammatory medicine (NSAIM); children and adolescents under 16 years (to reduce risk of Reye's syndrome); previous or active peptic ulceration; haemophilia and other bleeding disorders; not for treatment of gout.

Precautions:

- asthma
- allergic disease
- renal impairment
- hepatic impairment
- pregnancy
- breastfeeding
- older persons
- G6PD-deficiency
- dehydration interactions.

Dose:

Mild-to-moderate pain, pyrexia, by mouth with or after food, ADULT, 300–900 mg every 4–6 hours if necessary; maximum, 4 g daily; CHILD under 16 years, not recommended.

Mild-to-moderate pain, pyrexia, by rectum, ADULT, 600–900 mg inserted every 4 hours if necessary; maximum, 3.6 g daily; CHILD under 16 years, not recommended.

Inflammatory arthritis, by mouth with or after food, ADULT, 4–8 g daily in divided doses in acute conditions; up to 5.4 g daily may be sufficient in chronic conditions.

Adverse effects: generally mild and infrequent for lower doses, but common with anti-inflammatory doses; gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major haemorrhage); also other haemorrhage including subconjunctival; hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion, hypersensitivity reactions including angioedema, bronchospasm, and rash; increased bleeding time; rarely oedema, myocarditis and blood disorders (particularly thrombocytopenia).

2. CODEINE PHOSPHATE

Tablet: 15 mg, 30 mg, 60 mg

Oral solution: 25 mg/5 mL

Injection: 60 mg/mL

Medication subject to international control under the Single Convention on Narcotic Drugs, 1961.

NOTE: Codeine is a prodrug of morphine, requiring metabolism by CYP2D6 to morphine to provide an analgesic effect. Most of its analgesic effect results from the ≤10% of codeine which is converted to morphine by O-demethylation via CYP2D6 (*1*,*2*,*3*). There is a high degree of variability in CYP2D6 metabolism of codeine to morphine because of genetic differences between individuals and ethnic groups, making the benefits and risks of use unpredictable. On average, 77–92% of people extensively metabolize codeine to morphine while 5–10% are poor metabolizers and experience no analgesic benefit. The 1–2% of people who are ultra-rapid metabolizers are at the highest risk for morphine exposure and toxicity, including respiratory depression. Prevalence of ultra-rapid metabolizers varies considerably depending on ethnicity: Caucasian 1–10%; Arabs, Ethiopians and North Africans 16–28% (*4*). In 2015 the Ethiopian government temporarily banned codeine (*5*). In addition, some authorities assert that there is no pharmacological need for weak opioids such as codeine in cancer pain because low doses of morphine (or an alternative strong opioid) generally provide quicker and better relief from cancer pain (*6*,*7*). These authorities discourage any use of codeine (*3*).

Uses: mild-to-moderate pain; diarrhoea.

Contraindications: respiratory depression, obstructive airways disease, acute asthma attack; where there is risk of paralytic ileus.

Precautions:

- renal impairment
- hepatic impairment
- dependence
- pregnancy
- breastfeeding
- overdosage.

Interactions:

- alcohol: enhanced sedative and hypotensive effect
- amitriptyline: possibly increased sedation
- chlorpromazine: enhanced sedative and hypotensive effect
- clomipramine: possibly increased sedation
- diazepam: enhanced sedative effect
- fluphenazine: enhanced sedative and hypotensive effect
- haloperidol: enhanced sedative and hypotensive effect
- metoclopramide: antagonism of effect of metoclopramide on gastrointestinal activity
- ritonavir: possibly increases plasma concentration of codeine

Dose: mild-to-moderate pain, by mouth, ADULT, 30–60 mg every 4 hours when necessary; maximum, 240 mg daily.

Adverse effects: constipation particularly troublesome in long-term use; dizziness, nausea, vomiting; difficulty with micturition; ureteric or biliary spasm; dry mouth, headaches, sweating, facial flushing; in therapeutic doses, codeine is much less liable than morphine to produce tolerance, dependence, euphoria, sedation or other adverse effects.

3. FENTANYL

Transmucosal lozenge: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg (as citrate).

Transdermal patch (extended-release): 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr, (as base).

Injection: 50 mcg/mL in various vial sizes (as citrate)

Indications: moderate-to-severe persisting pain.

Contraindications: hypersensitivity to opioid agonists or to any component of the formulation; acute respiratory depression; acute asthma; paralytic ileus; concomitant use with, or use within 14 days after ending, monoamine oxidase inhibitor therapy; raised intracranial pressure and/or head injury, if ventilation not controlled; coma.

Precautions: impaired respiratory function; avoid rapid injection which may precipitate chest wall rigidity and difficulty with ventilation; bradycardia; asthma; hypotension; shock; obstructive or inflammatory bowel disorders; biliary tract disease; convulsive disorders; hypothyroidism; adrenocortical insufficiency; avoid abrupt withdrawal after prolonged treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis; (patches:) increased serum levels in patients with fever >40 °C (104 °F).

Skilled tasks: warn the patient or caregiver about the risk of undertaking tasks requiring attention or coordination, e.g. operating heavy machinery.

Dosage:

Starting dose for opioid-naive patients:

- SC/IV injection:
  - start with a stat dose of 25–100 mcg and then 25–50 mcg p.r.n.
  - reduce the dose in the elderly and debilitated, e.g. 12.5–25 mcg p.r.n.
  - traditionally p.r.n. dosing intervals are q1h, but more frequent dosing with close monitoring may be required in severe acute pain
  - give IV by slow injection over 3–5 minutes; this reduces the risk of muscular rigidity.
- Continuous SC/IV infusion:
  - initial dose 240–480 mcg/24h
  - for breakthrough pain, allow 10% of the 24h infusion dose p.r.n. q1h
  - titrate the infusion dose as needed
- Transdermal patch:
  - 12–25 mcg/h (See **Tables A6.3** and **6.4** below for conversion of morphine to fentanyl transdermal patch).

Dose for transmucosal lozenge (oral transmucosal fentanyl citrate): Start with lowest dose and use only for breakthrough pain in opioid-tolerant patients: patients on a regular strong opioid for chronic cancer pain for ≥1 week. The minimum dose of the regular strong opioid should be morphine 60 mg/24h PO, or fentanyl 25 mcg/h transdermal, or hydromorphone 8 mg/24h PO, or oxycodone 30 mg/24h PO, or

an equivalent dose of another opioid. Prescribers of transmucosal fentanyl products should:

- be experienced in the management of opioid therapy in cancer patients;
- limit use to patients who can adhere to the instructions regarding indication, administration, storage and returns;
- provide ongoing supervision;
- keep in mind the potential for fentanyl to be misused; and
- understand that the various transmucosal formulations are not bio-equivalent and not directly interchangeable, and thus:
  - prescribe by brand;
  - when starting or switching transmucosal products, de novo titration from the lowest available dose is required.

Adverse effects:

- common – nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, muscle rigidity, apnoea, myoclonic movements, bradycardia, hypotension, abdominal pain, anorexia, dyspepsia, mouth ulcer, taste disturbance, vasodilation, anxiety, drowsiness, diaphoresis;
- uncommon – flatulence, diarrhoea, laryngospasm, dyspnoea, hypoventilation, depersonalization, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, muscle weakness, hypertension, dizziness, itching, bronchospasm;
- rare – circulatory depression, cardiac arrest, hiccups, arrhythmia, paralytic ileus, haemoptysis, psychosis, seizures, shock, asystole, pyrexia, ataxia, muscle fasciculation, local irritation (with patches).

Interactions with other medicines:*

- amiodarone – profound bradycardia, sinus arrest and hypotension have been reported;
- beta-adrenergic blockers – severe hypotension reported;
- calcium channel blockers – severe hypotension reported;
- central nervous system depressants – additive or potentiating effects with fentanyl;
- imidazole antifungals – possible enhanced or prolonged effects of fentanyl;
- macrolide antibiotics – possible enhanced or prolonged effects of fentanyl;
- monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
- naloxone* – precipitates opioid withdrawal symptoms;

- naltrexone* – precipitates opioid withdrawal symptoms;
- neuroleptics – possible reduced pulmonary arterial pressure, hypotension and hypovolaemia;
- nitrous oxide – possible cardiovascular depression;
- opioid antagonists/partial agonists – may precipitate opioid withdrawal symptoms;
- phenytoin – may reduce plasma concentration of fentanyl; and
- protease inhibitors – possible enhanced or prolonged effects of fentanyl.

* Indicates severe.

4. HYDROMORPHONE

Injection: 1 mg/mL ampoule, 2 mg/mL ampoule, 4 mg/mL ampoule, 10 mg/mL ampoule (as hydrochloride)

Tablet: 2 mg, 4 mg, 8 mg (as hydrochloride)

Oral liquid: 1 mg (as hydrochloride)/mL

Sustained-release capsules: 2 mg, 4 mg, 8 mg, 16 mg, 24 mg

Indications: moderate-to-severe persisting pain.

Contraindications: hypersensitivity to opioid agonists or to any component of the formulation; acute respiratory depression; acute asthma; paralytic ileus; concomitant use with, or use within 14 days after ending, monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma.

Precautions: impaired respiratory function; avoid rapid injection which may precipitate chest wall rigidity and difficulty with ventilation; bradycardia; asthma; hypotension; shock; obstructive or inflammatory bowel disorders; biliary tract disease; convulsive disorders; hypothyroidism; adrenocortical insufficiency; avoid abrupt withdrawal after prolonged treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis.

Skilled tasks: warn the patient or caregiver about the risk of undertaking tasks requiring attention or coordination, e.g. operating heavy machinery.

Dosage:

Starting dose for opioid-naive patients:

- Oral: 1–4 mg every 4 hours as needed
- SC/IV injection: 0.3–0.7 mg every 3–4 hours as needed
- SC/IV continuous infusion: 0.1–0.2 mg/h.

Renal impairment: moderate (GFR 10–20 mL/min or serum creatinine 300–700 micromol/L) and severe (GFR <10 mL/min or serum creatinine >700 micromol/L) – reduce dose, start with lowest dose and titrate according to response.

Hepatic impairment: use with caution and reduce initial dose in all degrees of impairment.

Adverse effects:

- common – nausea, vomiting, constipation, dry mouth, sedation, biliary spasm, respiratory depression, muscle rigidity, apnoea, myoclonic movements, asthenia, dizziness, confusion, dysphoria, euphoria, light-headedness, pruritus, rash, somnolence, sweating;
- uncommon – hypotension, hypertension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, miosis, visual disturbances, abdominal cramps, anorexia, paraesthesia, malaise, agitation, tremor, muscle weakness, hallucinations, vertigo, mood changes, dependence, drowsiness, anxiety, sleep disturbances, headache, taste disturbance, agitation, urinary retention, laryngospasm, bronchospasm;
- rare – circulatory depression, cardiac arrest, respiratory arrest, shock, paralytic ileus, seizures.

Interactions with other medicines:

- central nervous system depressants – additive or potentiating effects with hydromorphone;
- ethanol* – additive or potentiating effects with hydromorphone, potential fatal interaction (dose dumping) if used with extended-release hydromorphone preparations;
- monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
- naloxone* – precipitates opioid withdrawal symptoms;
- naltrexone* – precipitates opioid withdrawal symptoms; and
- opioid antagonists/partial agonists* – may precipitate opioid withdrawal symptoms.

* Indicates severe.

5. IBUPROFEN

Tablet: 200 mg; 400 mg

Uses: pain and inflammation in rheumatic disease and other musculoskeletal disorders; mild-to-moderate pain including dysmenorrhoea and headache; acute migraine attack.

Contraindications: hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAIM; active peptic ulceration.

Precautions: renal impairment; hepatic impairment; preferably avoid if history of peptic ulceration; cardiac disease; older persons; pregnancy and breastfeeding; coagulation defects; allergic disorders; interactions.

Dose:

Mild-to-moderate pain, pyrexia, inflammatory musculoskeletal disorders, by mouth with or after food, ADULT, 1.2–1.8 g daily in 3–4 divided doses, increased if necessary to maximum 2.4 g daily (3.2 g daily in inflammatory disease); maintenance dose of 0.6–1.2 g daily may be sufficient.

Adverse effects: gastrointestinal disturbances, including nausea, diarrhoea, dyspepsia, ulceration, and haemorrhage; hypersensitivity reactions including rash, angioedema and bronchospasm; headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity, haematuria; fluid retention (rarely precipitating congestive heart failure in older persons), raised blood pressure, renal failure; rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic dermal necrolysis (Lyell syndrome), colitis and aseptic meningitis.

6. METHADONE

Injection: 10 mg/mL in various vial sizes (as hydrochloride)

Tablet: 5 mg, 10 mg, 40 mg (as hydrochloride)

Oral liquid: 1 mg/mL, 2 mg/mL, 5 mg/mL (as hydrochloride)

Oral concentrate: 10 mg/mL (as hydrochloride)

CAUTION: Due to the complex nature and wide inter-individual variation in the pharmacokinetics of methadone, methadone should be commenced only by practitioners experienced with its use.

Titration should be carried out with close clinical observation of the patient over several days.

Indications: moderate-to-severe persisting pain.

Contraindications: hypersensitivity to opioid agonists or to any component of the formulation; acute respiratory depression; acute asthma; paralytic ileus; concomitant use with, or use within 14 days after ending, monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma.

Precautions: impaired respiratory function; avoid rapid injection which may precipitate chest wall rigidity and difficulty with ventilation; history of cardiac conduction abnormalities; family history of sudden death (electrocardiograph [ECG] monitoring recommended); QT interval prolongation; asthma; hypotension; shock; obstructive

or inflammatory bowel disorders; biliary tract disease; convulsive disorders; hypothyroidism; adrenocortical insufficiency; avoid abrupt withdrawal after prolonged treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis.

Skilled tasks: warn the patient about the risk of undertaking tasks requiring attention or coordination, e.g. operating heavy machinery.

Dosage: In general, methadone should be reserved for patients who fail to respond well to morphine or another strong opioid. See **Table 1** and referenced documents for details on switching from other opioids to methadone (*3*). However, the following doses can be used for initiating methadone therapy in an opioid-naïve patient when necessary:

- 2.5 mg (1–2 mg in older persons) PO q8h regularly and q6h p.r.n.
- if necessary, titrate the regular dose upwards once a week, guided by p.r.n. use.

Renal impairment: severe (GFR <10 mL/min or serum creatinine >700 micromol/L) – reduce dose by 50% and titrate according to response; significant accumulation is not likely in renal failure, as elimination is primarily via the liver.

Hepatic impairment: avoid or reduce dose; may precipitate coma.

Adverse effects:

- common – nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, drowsiness, muscle rigidity, hypotension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dependence, confusion, urinary retention, ureteric spasm;
- uncommon – restlessness, dyspnoea, hypoventilation, depersonalization, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, muscle weakness, hypertension, dizziness, itching, bronchospasm, dysmenorrhoea, dry eyes, hyperprolactinaemia; and
- rare – QT interval prolongation, torsades de pointes, hypothermia, circulatory depression, cardiac arrest, hiccups, arrhythmia, paralytic ileus, haemoptysis, psychosis, seizures, shock, asystole, pyrexia, ataxia, muscle fasciculation, raised intracranial pressure.

Interactions with other medicines:

- abacavir – plasma concentration of methadone possibly reduced;
- amiodarone – may result in an increased risk of QT interval prolongation;
- atomoxetine – increased risk of ventricular arrhythmias;
- carbamazepine – plasma concentration of methadone reduced;

- central nervous system depressants – additive or potentiating effects with methadone;
- efavirenz – plasma concentration of methadone reduced;
- fluvoxamine – plasma concentration of methadone possibly increased;
- fosamprenavir – plasma concentration of methadone reduced;
- medicines that prolong the QT interval – may result in an increased risk of QT interval prolongation;
- monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
- naloxone* – precipitates opioid withdrawal symptoms;
- naltrexone* – precipitates opioid withdrawal symptoms;
- nelfinavir – plasma concentration of methadone reduced;
- nevirapine – plasma concentration of methadone possibly reduced;
- opioid antagonists/partial agonists – may precipitate opioid withdrawal symptoms;
- phenobarbital – plasma concentration of methadone reduced;
- phenytoin – metabolism of methadone accelerated by phenytoin resulting in reduced effect and risk of withdrawal symptoms;
- quinine – may result in an increased risk of QT interval prolongation;
- rifampicin – metabolism of methadone accelerated;
- ritonavir – plasma concentration of methadone reduced;
- voriconazole – plasma concentration of methadone increased; and
- zidovudine – methadone possibly increases zidovudine concentration.

* Indicates severe.

7. MORPHINE

Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule

Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 mL

Tablet: 10 mg (morphine sulfate)

Tablet (prolonged-release): 10 mg; 30 mg; 60 mg (morphine sulfate)

Medication subject to international control under the Single Convention on Narcotic Drugs, 1961.

Uses: moderate and severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia.

Contraindications: avoid in acute respiratory depression, acute alcoholism and where risk of paralytic ileus; also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: renal impairment and hepatic impairment; reduce dose or avoid in older and debilitated patients; hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy, pregnancy and breastfeeding. Severe withdrawal symptoms can develop if withdrawn abruptly.

Dose:

Acute pain, by subcutaneous injection (not suitable for oedematous patients), by intramuscular injection, or by intravenous injection: ADULT, 2–10 mg every 4 hours if necessary.

Chronic pain, by mouth (immediate-release tablets) or by subcutaneous injection (not suitable for oedematous patients) or by intravenous injection, ADULT, 2–20 mg regularly every 4 hours; dose may be increased according to need; oral dose should be approximately double the corresponding injected dose; by mouth (sustained-release tablets), titrate dose first using immediate-release preparation, then every 12 hours according to daily morphine requirement.

Myocardial infarction, by slow intravenous injection (2 mg/minute), ADULT, 5–10 mg followed by a further 5–10 mg if necessary; older or debilitated patients, reduce dose by half.

Acute pulmonary oedema, by slow intravenous injection (2 mg/minute), ADULT, 5–10 mg.

NOTE: The doses stated above refer equally to morphine sulfate and morphine hydrochloride. Sustained-release capsules designed for once-daily administration are also available [not included on the 15th World Health Organization (WHO) *Model list of essential medicines*; consult manufacturer's literature. Dosage requirements should be reviewed if the brand of controlled-release preparation is altered.

PATIENT ADVICE. Sustained-release tablets should be taken at regular intervals and not on an as-needed basis for episodic or breakthrough pain. Sustained-release tablets should not be crushed.

Adverse effects: nausea, vomiting (particularly in initial stages), constipation; drowsiness; also dry mouth, anorexia, spasm of urinary and biliary tract; bradycardia, tachycardia, palpitation, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, miosis; larger doses produce respiratory depression, hypotension, and muscle rigidity.

8. NALOXONE

Injection: 0.4 mg/mL (hydrochloride) in 1 mL ampoule

Indications: opioid overdose.

Contraindications: no contraindications to the use of naloxone for treatment of severe or life-threatening opioid toxicity such as respiratory depression.

Precautions: Cautious dosing is needed to avoid severe withdrawal syndrome after prolonged administration of opioids and in opioid-tolerant patients; cardiovascular disease; post-operative patients (may reverse analgesia and increase blood pressure).

Dosage:

- 0.08–0.12 mg IV every 2–3 minutes until the patient is breathing adequately
- After initial response, the intravenous dose may need to be repeated every 20–60 minutes because of the short duration of action
- For continuous intravenous infusion, dilute to a concentration of 4 mcg/mL with glucose 5% or sodium chloride 0.9%

Renal impairment: excretion of some opioids and/or their active metabolites (codeine, dextropropoxyphene, dihydrocodeine, morphine, pethidine, oxycodone) is delayed in impairment so these opioids will accumulate; extended treatment with naloxone infusion may be required to reverse opioid effect.

Hepatic impairment: no dose adjustment necessary.

Adverse effects:

- common – nausea, vomiting, sweating
- uncommon – tachycardia, ventricular arrhythmias
- rare – cardiac arrest.

Interactions with other medicines: there are no known interactions where it is advised to avoid concomitant use.

9. OXYCODONE

Tablet: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (as hydrochloride)

Tablet (modified-release): 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 160 mg (as hydrochloride)

Capsule: 5 mg, 10 mg, 20 mg (as hydrochloride)

Oral liquid: 1 mg/mL (as hydrochloride)

Concentrated oral liquid: 10 mg/mL, 20 mg/mL (as hydrochloride)

Indications: moderate-to-severe persisting pain.

Contraindications: hypersensitivity to opioid agonists or to any component of the formulation; acute respiratory depression; acute asthma; paralytic ileus; concomitant use with, or use within 14 days after ending, monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma.

Precautions: impaired respiratory function; avoid rapid injection which may precipitate chest wall rigidity and difficulty with ventilation; bradycardia; asthma; hypotension; shock; obstructive or inflammatory bowel disorders; biliary tract disease; convulsive disorders; hypothyroidism; adrenocortical insufficiency; avoid abrupt withdrawal after prolonged treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis.

Skilled tasks: warn the patient or caregiver about the risk of undertaking tasks requiring attention or coordination, e.g. operating heavy machinery.

Dosage for opioid-naïve patients:

- Immediate-release formulation: 2.5–5 mg PO q4h as needed; and
- For constant or frequently recurring pain, can use modified-release (sustained-release): 10 mg PO q12h, and add immediate release 2.5–5 mg PO q4h as needed for breakthrough pain.

Renal impairment: mild (GRF 20–50 mL/min or approximate serum creatinine 150–300 micromol/L) to severe (GFR <10mL/min or serum creatinine >700 micromol/L) – dose reduction may be required; start with lowest dose and titrate according to response.

Hepatic impairment: moderate and severe; reduce dose by 50% or avoid use.

Adverse effects:

- common – nausea, vomiting, constipation, diarrhoea, dry mouth, sedation, biliary spasm, abdominal pain, anorexia, dyspepsia, pruritus, somnolence, dizziness;
- less common – muscle rigidity, hypotension, respiratory depression, bronchospasm, dyspnoea, impaired cough reflex, asthenia, anxiety, chills, muscle fasciculation, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dizziness, confusion;
- uncommon – bradycardia, tachycardia, palpitation, oedema, mood changes, dependence, drowsiness, sleep disturbances, headache, miosis, visual disturbances, sweating, flushing, rash, urticaria, restlessness, difficulty with micturition, urinary retention, ureteric spasm, gastritis, flatulence, dysphagia, taste disturbance, belching, hiccups, vasodilation, supraventricular tachycardia, syncope, amnesia, hypoesthesia, pyrexia, amenorrhoea, hypotonia, paraesthesia, disorientation, malaise, agitation, speech disorder, tremor, dry skin;

- rare – raised intracranial pressure, circulatory depression, cardiac arrest, respiratory arrest, shock, paralytic ileus, seizures.

Interactions with other medicines:

- central nervous system depressants – additive or potentiating effects with oxycodone;
- monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
- naloxone* – precipitates opioid withdrawal symptoms;
- naltrexone* – precipitates opioid withdrawal symptoms; and
- opioid antagonists/partial agonists* – may precipitate opioid withdrawal symptoms.

* Indicates severe.

10. PARACETAMOL

Oral liquid: 120 mg/5 mL

Suppository: 100 mg

Tablet: 100–500 mg

Injection (for IV infusion): 10 mg/mL

Uses: mild-to-moderate pain, including dysmenorrhoea and headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including postimmunization pyrexia; acute migraine attack.

Precautions: hepatic impairment; renal impairment; alcohol dependence; breastfeeding. Unintentional overdose of paracetamol resulting in hepatotoxicity and death can occur. To reduce this risk, the dose of paracetamol should not exceed the maximum recommended dose, should be appropriate for the weight of the patient, and should be reduced when risk factors for hepatotoxicity exist.

Dose:

Mild-to-moderate pain, pyrexia, by mouth or by rectum, ADULT, 0.5–1 g every 4–6 hours, maximum 4 g daily.

IV paracetamol can be used when administration Per Oral or Per Rectal is not possible. The dose depends on body weight and the presence/absence of risk factors for paracetamol hepatotoxicity:

- >50 kg, 1 g up to q4h, maximum recommended dose 4 g/24h
- >50 kg plus any risk factors, restrict maximum dose to 3 g/24h
- 10–50 kg, 15 mg/kg up to q4h, maximum recommended dose 60 mg/kg/24h.

For patients with severe renal impairment, (creatinine clearance <30 mL/min) the minimum interval must be ≥q6h.

Adverse effects: rare but rash and blood disorders reported; important: liver damage (and less frequently renal damage) following overdosage.

II. TYPICAL STARTING DOSES

Typical starting doses of pain medicines are provided in **Table A6.1**. Like the pain assessment tables and the analgesic ladder provided in **Annex 1**, these are tools that may be useful in clinical care. However, safe and effective cancer pain treatment requires careful assessment of each individual patient's pain and individualized therapeutic planning.

Table A6.1. Typical starting doses of selected medicines for chronic cancer pain in adults with no kidney or liver disease

MEDICINE	TYPICAL STARTING DOSE	NOTES
Paracematol	500–1000 mg orally every 6 hours	Maximum dose 1000 mg orally every 6 hours.
Ibuprofen	400–800 mg orally every 8 hours	Take with food and consider adding proton pump inhibitor to reduce gastrointestinal toxicity. Avoid in patients with bleeding risk or thrombocytopenia. Maximum dose 800 mg orally every 8 hours.
Morphine	5 mg orally every 4 hours 2 mg IV/SC every 4 hours	No maximum dose.
Fentanyl	12–25 mcg/hr transdermal patch every 72 hours	Do not use in patients with severe cachexia, fevers or frequent sweating. No maximum dose.
Amitriptyline	10–25 mg orally at bedtime	Anticholinergic side-effects including orthostatic hypotension, sedation, confusion, tachycardia, constipation, dry mouth. Maximum dose 100 mg orally at bedtime where blood levels cannot be checked.

Source: Adapted from Cherny et al. 2015 (*30*).

III. OPIOID CONVERSION TABLES

NOTE: Adapted with permission from Twycross et al. 2017 (*3*).

The ability judiciously, safely and effectively to change a patient's pain treatment from one opioid to another can be of great clinical importance. For instance, this skill can help to prevent or minimize opioid toxicity, other adverse effects or drug interactions, while maintaining or improving analgesia. However, no randomized controlled trials (RCTs) of opioid switching have been conducted, and existing conversion tables are based on generally weak evidence from retrospective or observational studies (*8*). Conversion ratios can never be more than an approximate guide for several reasons (*9*,*10*):

- wide inter-individual variation in opioid pharmacokinetics;
- clinical factors such as age, haemodynamic stability, renal and hepatic function, nutritional status and concurrent medications;
- other variables, including dose and duration of opioid treatment and direction of switch in opioid; and
- their method of derivation (e.g. single dose rather than chronic dose studies using a range of clinical doses).

Thus, careful clinical monitoring during conversion is necessary to avoid under-dosing, excessive dosing and adverse effects, especially when switching at high doses, when rapidly increasing the dose of the first opioid, and when switching to methadone. However, conversion tables can and should inform clinical judgement about switching opioids and can help clinicians to avoid gross miscalculations. We provide here two examples of opioid equi-analgesic conversion tables (**A6.2** and **A6.3**) that are adapted from a leading publication on this topic (*3*). They are presented merely as examples and should not be construed as recommended by WHO. A dose reduction of around 50% of the calculated equivalent dose of the new opioid is prudent when switching at high doses (e.g. morphine or equivalent doses of ≥ 1 g/24h), in elderly or frail patients, because of intolerable undesirable effects (e.g. delirium), or when there has been a recent rapid escalation of the first opioid (possibly due to opioid-induced hyperalgesia). In such circumstances, "as needed" doses can be relied on to make up any deficit while re-titrating to a satisfactory dose of the new opioid.

Table A6.2. Approximate potency of opioids relative to morphine; PO and immediate-release formulations unless stated otherwise[a]

ANALGESIC	POTENCY RELATIVE TO MORPHINE	DURATION OF ACTION (HOURS)[b]
Codeine Dihydrocodeine	1/10	3–6
Pethidine	1/8	2–4
Tapentadol	1/3	4–6
Hydrocodone (not United Kingdom)	2/3	4–8
Oxycodone	1.5 (2)[c]	3–4
Methadone	5–10[d]	8–12
Hydromorphone	4–5 (5–7.5)[d]	4–5
Buprenorphine (SL)	80	6–8
Buprenorphine (TD)	100 (75–115)[c]	Formulation dependent (72–168)
Fentanyl (TD)	100 (150)[c]	72

Source: Adapted with permission from Twycross et al. 2017:371 (Table 4) (*3*).

[a] Multiply dose of opioid in the first column by relative potency in the second column to determine the equivalent dose of morphine sulfate/hydrochloride; conversely, divide morphine dose by the relative potency to determine the equivalent dose of another opioid.

[b] Dependent in part on severity of pain and on dose; often longer-lasting in very elderly and those with renal impairment.

[c] The numbers in parenthesis are the manufacturers' preferred relative potencies.

[d] A single 5 mg dose of methadone is equivalent to morphine 7.5 mg, but a variable long plasma half-life and broad-spectrum receptor affinity result in a much higher-than-expected relative potency when administered regularly – sometimes much higher than the range given above. Therefore, guidance from a specialist is recommended for conversions to regularly administered methadone.

Table A6.3. Recommended dose conversion ratios; PO to SC/IV

CONVERSION	RATIO	CALCULATION	EXAMPLE
Hydromorphone to hydromorphone	3:1[a]	Divide 24h hydromorphone dose by 3	Hydromorphone 32 mg/24h PO → hydromorphone 10 mg/24h SC/IV
Methadone to methadone	2:1[b]	Divide 24h methadone dose by 2	Methadone 30 mg/24h PO → methadone 15 mg/24h SC/IV
Morphine to fentanyl	Variable[c,d]	Divide 24h morphine dose in mg by 100–150	Morphine 60 mg/24h PO → fentanyl 400 mcg/24h SC/IV
Morphine to hydromorphone	10:1	Divide 24h morphine dose by 10	Morphine 60 mg/24h PO → hydromorphone 6 mg/24h SC/IV
Morphine to morphine	2:1	Divide 24h morphine dose by 2	Morphine 60 mg/24h PO → morphine 30 mg/24h SC/IV

Source: Adapted with permission from Twycross et al. 2017:861 (Table 3) (*3*).

[a] Manufacturer's recommendation. Because mean oral bio-availability is 50% (range 35–60%), some centres use a conversion ratio of 2:1 rather than 3:1.

[b] Because mean oral bio-availability is 80% (range 40–100%), some centres use 1:1, e.g. methadone 30 mg/24h PO → methadone 30 mg/24h SC/IV.

[c] The same conversion ratios as for morphine PO to fentanyl TD can be used for morphine PO to fentanyl SC/IV.

[d] Volume constraints for a syringe driver may prevent doses >500 mcg/24h being used.

Table A6.4. Comparative doses of PO morphine and TD fentanyl (based on dose conversion ratio 100:1)

PO MORPHINE	SC/IV MORPHINE	TD FENTANYL	
mg/24h	**mg/24h[a]**	**mcg/h**	**mg/24h**
30	15	12	0.3
60	30	25	0.6
90	45	37.5	0.9
120	60	50	1.2
180	90	75	1.8
240	120	100	2.4

Source: Adapted with permission from Twycross et al. 2017:417 (*3*).

[a] The assumption is that morphine SC/IV is twice as potent as PO.

IV. OPIOID CESSATION

High-quality evidence for opioid tapering protocols is lacking. Opioid tapering should be individualized depending on the clinical situation. For patients who do not have a substance use disorder, **Table A6.5** provides a general strategy for opioid tapering when opioid therapy is no longer indicated (*10*).

Table A6.5. Strategies for cessation of opioid therapy in various clinical situations

CLINICAL SITUATION	TAPERING AND CESSATION STRATEGY	NOTES
Short-term use (less than 2 weeks)	■ Taper needed only if residual pain persists. ■ If the cause of pain has been fully treated, can discontinue opioid therapy immediately without tapering.	Physical dependence highly unlikely.
Long-term use (more than 1 month)	■ Taper by 10% per week. ■ If symptoms or signs of opioid withdrawal occur (e.g. drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhoea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection), increase to the previous highest dose and change taper to 10% every two weeks. ■ Once the smallest available dose is reached, extend the interval between doses. Discontinue opioid when dosing interval reaches 24 hours without signs or symptoms of withdrawal.	Some degree of physical dependence likely.
Use between 2 and 4 weeks	■ Taper by 10–50% per week. ■ If symptoms or signs of opioid withdrawal occur (e.g. drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhoea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection), increase to the previous highest dose and reduce the percentage of each taper. ■ Once the smallest available dose is reached, extend the interval between doses. Discontinue opioid when dosing interval reaches 24 hours without signs or symptoms of withdrawal.	Physical dependence uncertain.
Long-term use and substance use disorder	■ Consult specialist in opioid use disorders if possible. ■ Consider treatment of opioid use disorder as part of tapering strategy.	

Source: Adapted from Dowell 2016 (*10*).

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ANNEX 7: NETWORK META-ANALYSIS OF EVIDENCE COMPARING ANALGESICS FOR CANCER PAIN MANAGEMENT INITIATION & MAINTENANCE AND FOR BREAKTHROUGH CANCER PAIN

Available online at:
https://www.who.int/ncds/management/palliative-care/Cancer-pain-guidelines-Annex-7.pdf

ANNEX 8: GLOSSARY

Adjuvant: Medicines other than opioids, paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) that may help to relieve pain alone or in combination with opioids, paracetamol or NSAIDs. Typically used for neuropathic pain refractory to opioids, paracetamol or NSAIDs or when opioid therapy is contraindicated.

Breakthrough pain: Transitory flare of pain despite pain treatment around-the-clock.

Clinical trial: An experiment performed on human beings in order to evaluate the comparative efficacy of two or more therapies.

Co-formulation (of analgesia): This is a packaged medicine which contains two or more analgesic drugs packaged together as a single medicine.

Immediate-release medicine: Medicine that has rapid onset of action and short duration of action.

Non-opioid: Substances that relieve pain without acting on opioid receptors (see Opioid).

Older persons: Persons older than 60 years.

Opioid: Substances derived from the opium poppy or synthesized that act on opioid receptors in the central or peripheral nervous system to produce pain relief.

- Weak opioid: opioid with weak pain relief effect.
- Strong opioid: opioid with strong pain relief effect.
- Opioid rotation: switching from one opioid medicine to another for a therapeutic purpose.

Rescue dose: An extra dose of pain medicine to treat breakthrough pain (see Breakthrough pain).

Slow-release medicine: Medicine that has a slow onset of action and long duration of action.

Trial of therapy: A clinical decision to provide a medicine or treatment of potential (but unproven) benefit to an individual patient to assess if there is a beneficial response.

WHO GUIDELINES FOR THE PHARMACOLOGICAL AND RADIOTHERAPEUTIC MANAGEMENT OF **CANCER PAIN** IN ADULTS AND ADOLESCENTS

World Health Organization

20 Avenue Appia
CH-1211 Geneva 27
Switzerland
www.who.int/

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