

# **SCOPING DOCUMENT FOR WHO Treatment Guidelines on pain related to cancer, HIV and other progressive life-threatening illnesses in adults**

## **BACKGROUND**

The justification for developing these guidelines lies in the need to update existing guidelines for cancer pain management. Published in 1996 (1), some aspects are now out of date as new drugs have come on the market whilst others have dropped out of common clinical practice. The Delphi study conducted in June 2007 (2) confirms that experts and professional bodies related to pain are looking to the World Health Organization (WHO) to take a lead in this development.

Whilst recognising that pain control is only a component of the much wider scope of palliative care in people with cancer, HIV and other progressive life-threatening illnesses, these guidelines could serve as a guide to health care professionals, policy makers and regulatory authorities for facilitating legal access and ensuring proper use of analgesics and other modalities to achieve rapid, effective and safe pain control. The guidelines will be jointly developed by the *Access to Controlled Medicines Programme*, the *Cancer Control Programme*, *Management of Mental and Brain Disorders*, *Clinical Procedures* and *Child and Adolescent Health and Development*.

This scoping document sets out:

- the overall objective of these guidelines
- the types of patients to whom the guidelines apply
- the outcomes that are sought
- the proposed table of contents for the publication, and
- the clinical questions for which evidence needs to be sought and appraised so that evidence-based recommendations can be made.

The full guidelines should be developed in accordance with the principles for clinical guidelines laid down by the WHO Guideline Review committee.

## **OBJECTIVES AND PATIENT POPULATION**

The overall objective of these guidelines is to provide evidence-based recommendations that, if followed, will improve the pain experience of adult patients with chronic pain related to cancer, HIV/AIDS, progressive life-threatening illnesses and organ failure. These conditions were identified because they cause significant global burden now and are set to rise (see table 1).

Some therapies which contribute to the improvement of the pain experience are beyond the scope of this document. These include disease-modifying therapies (e.g. anti-cancer therapies, anti-retroviral therapies), These would be addressed by other WHO guidelines and reference /linkages will be made to them as needed.

Patient population: These guidelines address adults and adolescents (i.e. people aged 11-18 years) with chronic pain related to malignant conditions (cancer), HIV/AIDS, and other progressive diseases. Since pharmacology for adolescents is similar to adult, management of pain related to cancer, HIV, and other life threatening illnesses in adolescents is included in this guideline.

The critical outcomes that should be considered include: effectiveness of pain relief, and maintenance of pain reduction, cost effectiveness, speed at which pain reduction may be achieved, maintenance of pain relief, effect on quality of life, effect on an individual's function, anxiety and mood, adverse effects, complications of treatments/interventions and risk-benefit analysis of interventions for pain relief.

**Table 1 Disability-adjusted Life Years (DALYs) in 2002 and projections to 2030**

*Source: Mathers & Loncar 2006 (3)*

Diseases	Total DALYs ('000)	
	2002	2030 (baseline projection)
Malignant neoplasms	75,336	105,001
HIV/AIDS	82,380	185,923
Cardiovascular	148,985	176,999
Chronic obstructive pulmonary disease	28,049	48,369
Diabetes	16,165	29,715
Alzheimer and other dementias	10,392	18,394

## PROPOSED TABLE OF CONTENTS

### A. Executive summary

The objective of these guidelines, the patients to whom they apply, the target audience and key recommendations should be stated.

Acknowledgment would be included before the executive summary.

## B. Introduction

This should include:

- a clear statement on the overall objective of these guidelines and the patients to whom these guidelines are meant to apply
- a statement on target audience: who will use these guidelines - physicians, nurses, physician assistant, clinicians, specialists, general practitioners, pharmacists, caring for adults. It also aims at policy makers and programme managers, who may not be involved directly in providing care, nevertheless play an important role in ensuring care of patients
- a clear statement on what is beyond the scope of this document
- a description of the biopsychosocial context in which these guidelines are contained - in particular the wider context of palliative care, the importance of holistic care of patients and their families and the recognition of pain as only one of many symptoms and areas of concern for patients with these diseases (with reference to other key documents relating to palliative care: ref 4, 5 and 6)
- the concept of total pain based on IASP and WHO definitions including the psychological, emotional, cultural and social sequelae of living with chronic pain over prolonged periods of time
- the recognition that much of pain management can be carried out in primary care and the community, with only a relatively small percentage of patients requiring specialist pain management
- the effectiveness of a coordinated team approach, in its broadest sense, i.e. depending on the resources available and the setting in which pain is being managed, teams may vary in composition (different disciplines, professions and combinations of professionals and non-professionals), complexity and size.

## C. Causes and classification of pain

This should be a brief section (maximum one page) to state:

- a definition and diagnostic features of the following:
  - nociceptive pain – including somatic, visceral, musculoskeletal pain
  - neuropathic pain
  - breakthrough or episodic pain
  - malignant vs non-malignant pain
  - acute vs chronic pain
  - pain at rest and pain on movement
  - mixed pain (nociceptive and neuropathic components together)
- the key investigations/actors which can be helpful in distinguishing between different causes/types of pain

- a recognition that there might be more than one cause of pain in patients with cancer and other life limiting illness and the importance of being able to identify them.

#### D. Evaluation of pain

This should include:

- reiteration of the concept of total pain
- recommendation about the steps which should be taken in a holistic assessment and documentation of pain, including assessment of cause, severity, activity and sleep disturbance, mood (anxiety, depression etc) and social impact
- the importance of systematic evaluation using validated tools, and the need for frequent reassessment
- recognition that there is a need to evaluate, measure and monitor pain and pain control and that a variety of pain scales are available though not one has been shown to be superior to others across all settings
- description of the evidence underpinning a selection of frequently used validated pain scales and the settings in which each has been validated for use (these pain scales to appear in annex)
- recognition that patients often do not report pain – for a variety of reasons including religion, finance, fear, culture (see ref 2, annex 4)
- recognition that health workers often underestimate and under treat patients' pain. and the role of skilled listening by health workers.

#### E. Treatment strategy

This should include a statement of the principles of treatment, e.g.:

- oral medicines are among the key components of pain management
- some medicines should be given regularly ("by the clock")
- a recognition that therapeutic regimes need to be individualised with attention to detail
- provision should be made for breakthrough or intermittent pain
- the necessity to monitor and evaluate for therapeutic and unwanted effects

This section should be divided into two main sections:

- Medicinal therapy: non-opioid medicines, opioid analgesics, co-analgesics and adjuvant medicines, rescue medicines, routes of administration, efficacy, safety, cost effectiveness, limitations, benefits, side effects.
- Non-medicinal therapy: explanation, beliefs, education, physical therapy, peripheral stimulation therapy (eg. transdermal electronic nerve stimulation (TENS), acupuncture), nerve blocks, radiotherapy, psychological therapy (cognitive behavioural therapy), supportive therapy (occupational therapy, employment etc).

The recommendations should be based on evidence sought and appraised in response to clinical questions 1 – 20 (see below). The formatting of this section could be as follows: preamble or introductory paragraph, followed by tabulated evidence leading to statement of recommendation.

#### F. System issues

The content of this section should flow from the evidence-based recommendations in the treatment section as well as evidence sought and appraised in response to the systems questions 21 - 23 (see below).

This section should include:

- a specific recommendation (which flows from the treatment recommendations) listing the key medications which should be available for pain relief at primary, secondary and tertiary levels
- a cost-analysis of the health system inputs that are required in order to achieve the critical outcomes for this patient population
- a recommendation on the skills required to prescribe treatment to adults with chronic pain related to cancer, HIV and other life-threatening diseases
- a statement about the safeguards that are useful to enable opioids to be safely and reliably administered to those who require this for effective pain control, whilst minimising the risk of drug diversion
- how health systems should balance the availability of prescription opioids for pain with prevention of prescription opioid abuse and dependence
- key policy, legislative, regulatory issues that ensures opioid availability across all levels of care, including:
  - a statement about facts and myths about medical use of opioid tolerance, and dependence
  - a statement about the safeguards that are useful to enable opioids to be safely and reliably administered to those who require this for effective pain control, whilst minimising the risk of drug diversion.

#### G. Annexes

- Selection of frequently used pain scales measuring pain intensity and pain relief, including those which are particularly suitable for specific groups, e.g. patients with dementia/learning disability.
- Opioid analgesic conversion table
- Opioid analgesic half-life table
- Evidence tables and other background materials
- Research agenda
- Membership of Expanded Review Panel (ERP) and Guideline Advisory Group and involved WHO staff.

## CLINICAL QUESTIONS

Evidence should be sought, critically appraised and synthesized before recommendations are formulated in response to these questions. Each question and its related sub-questions should lead to a specific recommendation.

### *Analgesic ladder*

- 1 In patients with nociceptive and neuropathic pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for using the 2-step analgesic ladder compared to the 3-step analgesic ladder in order to achieve rapid, effective and safe pain control?
- 2 In patients with nociceptive and neuropathic pain, what is the evidence to support the use of paracetamol as compared to aspirin and NSAIDs at each step of the analgesic ladder in terms of benefit against adverse effects in order to achieve and maintain rapid, effective and safe pain control?
- 3 If the evidence supports the continuing use of a 3-step analgesic ladder, what is the evidence to support the use of codeine as compared to tramadol at step 2 of the analgesic ladder, in terms of benefit balanced against adverse effects such as constipation, nausea and vomiting, sedation and confusion, in order to achieve and maintain rapid, effective and safe pain control?

### *Choice of strong opioids*

- 4 In patients with nociceptive and neuropathic pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence to support the use of morphine as the gold standard for strong opioids, in comparison to the use of other strong opioids (in particular fentanyl, hydromorphone, oxycodone and methadone), in terms of efficacy, adverse effects (such as constipation, nausea and vomiting, sedation and confusion) and cost-benefit in order to achieve and maintain rapid, effective and safe pain control?
- 5 In patients with nociceptive and neuropathic pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the practice of opioid rotation or opioid switching as compared to continuing use of one opioid in order to maintain effective and safe pain control?

### *Fears*

- 6 In patients with pain related to advancing and end-stage disease in cancer, HIV, progressive neurological diseases and organ failure, what is the risk of hastening

death when strong opioids are properly prescribed for pain control as compared to a similar group of patients who are not taking opioids? (see ref 7)

- 7 In patients with pain related to advancing and end-stage disease in cancer, HIV, progressive neurological diseases and organ failure, what is the risk of:
- developing tolerance
  - developing dependence
  - developing respiratory depression
- from taking regular or intermittent morphine for pain control as compared to a similar group of patients who are not taking opioids?
- 8 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence that the use of opioids could influence a person's performance when taken regularly to achieve and maintain pain control as compared to a similar group of patients who are not taking opioids?

#### *Administration of opioids*

- 9 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the benefit of administering modified-release morphine regularly as compared to immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?
- 10 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence, by age groups, for the benefit of using immediate release morphine as the top-up as-required analgesic of choice (in addition to regular background analgesia), as compared to other strong opioids in order to maintain effective and safe control of episodic or breakthrough pain?
- 11 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the benefit of using the oral route as compared to parenteral administration for opioids in order to achieve rapid, effective and safe pain control?
- 12 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the benefit of using the subcutaneous or transdermal route as compared to the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. patients with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?
- 13 What is the evidence for the recommendation that a double dose of immediate release morphine should be given at bedtime for those taking 4-hourly immediate

release morphine during the day as their regular analgesic in order to maintain effective pain control through the night?

*Co-analgesic and adjuvant medications*

- 14 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the use of steroids as compared to placebo in order to achieve and maintain effective and safe pain control?
- 15 In patients with muscle spasm pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the use of muscle relaxants such as diazepam as compared to baclofen and to placebo in order to achieve and maintain effective and safe pain control?
- 16 In patients with bone pain related to cancer, HIV, progressive neurological diseases and organ failure:
  - 16.1 what is the evidence for the use of non-selective NSAIDs as compared to placebo in order to achieve rapid, effective and safe control of bone pain?
  - 16.2 what is the evidence for the use of bisphosphonates as compared to placebo and in which specific subsets of patients, in order to achieve rapid, effective and safe control of bone pain
- 17 In patients with neuropathic pain related to cancer, HIV, progressive neurological diseases and organ failure:
  - 17.1 What is the evidence for the use of amitriptyline and other tricyclic antidepressants as compared to SSRIs in order to achieve rapid, effective and safe pain control?
  - 17.2 What is the evidence for the use of second generation anti-epileptics such as gabapentin as compared to first generation anti-epileptics such as carbamazepine or sodium valproate in order to achieve rapid, effective and safe pain control?
  - 17.3 What is the evidence for the use of second generation anti-epileptics such as gabapentin as compared to first generation anti-epileptics such as carbamazepine or sodium valproate in order to achieve rapid, effective and safe pain control?
  - 17.4 What is the evidence for the use of second generation anti-epileptics such as gabapentin as compared to placebo in order to achieve rapid, effective and safe pain control?
  - 17.5 What is the evidence for the use of NMDA receptor antagonists (e.g. ketamine) as compared to placebo in order to achieve rapid, effective and safe pain control?
  - 17.6 What is the evidence for the use of local anaesthetic agents as compared to placebo in order to achieve rapid, effective and safe pain control?

- 18 In patients with bone pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the use of radioactive isotopes, as compared to placebo in order to achieve rapid, effective and safe pain control?

*Non-drug therapies*

- 19 In patients with bone pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the use of radiotherapy as compared to placebo in order to achieve rapid, effective and safe pain control?
- 20 In patients with pain related to cancer, HIV, progressive neurological diseases and organ failure, what is the evidence for the use of nerve blocks and other interventional therapies as compared to placebo in order to achieve rapid, effective and safe pain control?

**SYSTEMS QUESTIONS**

- 21 In the management of pain in patients with cancer, HIV, progressive neurological diseases and organ failure, what evidence is there to support the practice of shifting the task of prescribing, titrating and monitoring analgesics from medically-qualified professionals to other professionals at different levels of care in order to ensure that rapid, effective and safe pain control can be achieved for all those who need it?
- 22 If the evidence supports the practice of task-shifting, what are the safeguards that need to be in place, in particular training and continuing supervision, and the resources required to provide and maintain these safeguards?
- 23 In the management of pain in patients with cancer, HIV, progressive neurological diseases and organ failure, what evidence is there about the level of pain management that can be provided at the primary care or generalist level, as compared to specialist level, in order to ensure that rapid, effective and safe pain control can be achieved for all those who need it?

## REFERENCES

1. Cancer Pain Relief – with a guide to opioid availability, second edition. WHO Geneva, 1996.
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4. Palliative care: symptom management and end of life care. Integrated guidelines for first-level facility health workers in low-resource settings. Integrated Management of Adolescent and Adult Illness (IMAI) Project, WHO, 2004. [http://ftp.who.int/htm/IMAI/Modules/IMAI\\_palliative.pdf](http://ftp.who.int/htm/IMAI/Modules/IMAI_palliative.pdf). Accessed 23 Nov 07.
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