WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses

World Health Organization

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- the Expanded Review Panel in defining the scope of the guidelines and in reviewing the evidence retrieval report;
- the Guidelines Development Group in reviewing and appraising the available evidence, formulating the recommendations, and defining the core principles on assessment, evaluation and treatment of pain;
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- the WHO Steering Group on Pain Treatment Guidelines.

For full membership lists see Annex 7.

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ATC	Anatomical Therapeutic Chemical Code (classification of medicines)
EMLc	WHO Model List of Essential Medicines for Children
ERP	Expanded Review Panel
GDG	Guidelines Development Group
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
IM	intramuscular
INCB	International Narcotics Control Board
ITT	intention to treat
IV	intravenous
mcg	microgram
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PCA	patient controlled analgesia
RCT	randomized control trial
SC	subcutaneous
SCD	sickle cell disease
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
VAS	visual analogue scale
WHO	World Health Organization

GLOSSARY

Adjuvant analgesic: medicine which has a primary indication other than pain, but is analgesic in some painful conditions. This excludes medicines administered primarily to manage adverse effects associated with analgesics, such as laxatives and anti-emetics.

Adolescent: a person from 10 to 18 years of age.

Analgesic (medicine): medicine that relieves or reduces pain.

Anatomical Therapeutic Chemical (ATC) Code: classification system of medicines into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.

Breakthrough pain: temporary increase in the severity of pain over and above the pre-existing baseline pain level.

Child: the narrow definition for children is from 1 to 9 years of age. However in these guidelines, the term children is used in a larger sense to comprise neonates, infants and often adolescents.

Controlled medicines: medicines that contain controlled substances.

Controlled substances: the substances listed in the international drug control conventions.

Dependence syndrome: a cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use, and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, and a higher priority given to drug use than to other activities and obligations (ICD-10 definition).

Dispersible tablets (oral solid formulation): uncoated or film-coated tablets that can be dispersed in liquid for administration as a homogenous dispersion. They can be dissolved, dispersed or mixed with food, in a small amount of water or breast milk prior to administration. They can be used in very young children (0–6 months), and require minimal manipulation from health-care providers and caregivers for administration, which minimizes the risk of errors.

End of dose pain: pain occurring when the blood level of the medicine falls below the minimal effective analgesic level towards the end of a dosing interval.

Enzyme CYP2D6: an important enzyme involved in the metabolism of medicines.

Idiopathic: adjective used primarily in medicine meaning arising spontaneously or from an obscure or unknown cause.

Idiopathic pain: pain for which the pathophysiological mechanisms are not identified.

Incident pain (or pain due to movement): pain that can be induced by simple movements such as walking, or a manoeuvre that would normally exacerbate pain, e.g. weight bearing on an extremity or pain during diagnostic or therapeutic procedures. Incident pain can occur during physical movements such as coughing or bladder spasm after urination.

Infant: a person from 29 days up to 12 months of age.

International drug control conventions: the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the Convention on Psychotropic Substances of 1971, and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

Narcotic drugs: a legal term that refers to all those substances listed in the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol.

Neonate: a person from zero to 28 days of age.

Neuropathic pain: pain caused by structural damage and/or nerve cell dysfunction in either the peripheral or central nervous system (CNS). Pain is persistent even without ongoing stimuli.

Pain assessment tools: tools used to assess pain intensity or, in addition, other features of pain such as location, characteristics, frequency. Pain intensity measurement tools are often referred to as pain scales. Alternative terms are pain assessment instrument, method or measure.

Pain intensity: term is used interchangeably with pain severity and referring to the level of pain experienced and reported by the patient.

Pain severity: term is used interchangeably with pain intensity and referring to the level of pain experienced and reported by the patient.

Persisting pain: term as used in these guidelines is intended to cover long-term pain related to medical illness, for example pain associated with major infections (e.g. HIV), cancer, chronic neuropathic pain (e.g. following amputation), and episodic pain (e.g. in sickle cell crisis). For a full explanation of the type of pain covered, please refer to the Introduction. For explanations on different classification systems of pain, refer to Chapter 1. *Classification of pain in children*.

Prolonged-release (formulation): term is used interchangeably with sustained-release, slow-release, extended-release and controlled-release.

Psychometrics: field of study concerned with the theory and technique of educational and psychological measurement, which includes the measurement of knowledge, abilities, attitudes, and personality traits. The field is primarily concerned with the construction and validation of measurement instruments, such as questionnaires, tests and personality assessments.

Rotation of opioids: for the purposes of these guidelines, rotation (or routine rotation) of opioids is defined as the clinical practice of changing between different opioids in a set schedule, not in response to a clinical problem, such as a side-effect, but as a preventive measure to limit future potential side-effects and dose escalation in patients that are anticipated to require long-term opioid therapy.

Switching of opioids: for the purposes of these guidelines, switching of opioids is defined as the clinical practice of changing to an alternative opioid because of dose-limiting side-effects and/or lack of analgesic effect.

Tolerance: a reduction in the sensitivity to a pharmacological agent following repeated administration. As a consequence, increased doses are required to produce the same magnitude of effect.

Withdrawal syndrome: the occurrence of a complex (syndrome) of unpleasant symptoms or physiological changes caused by an abrupt discontinuation or a dosage decrease after repeated administration of a pharmacological agent. Withdrawal syndrome can also be caused by the administration of an antagonist.

EXECUTIVE SUMMARY

Pain in children is a public health concern of major significance in most parts of the world. Although the means and knowledge to relieve pain exists, children's pain is often not recognized, is ignored or even denied. These guidelines address the pharmacological management of persisting pain in children with medical illnesses. As such, they replace the previous guidelines, *Cancer pain relief and palliative care in children,* which exclusively covered cancer pain. They include several clinical recommendations, including a new **two-step approach** of pharmacological treatment. The guidelines also point to the necessary policy changes required and highlight future priority areas of research.

Clinical and policy recommendations

An overview of clinical recommendations is provided on pages 146 and 147. All moderate and severe pain in children should always be addressed. Depending on the situation, the treatment of moderate to severe pain may include non-pharmacological methods, treatment with non-opioid analgesics and with opioid analgesics. These clinical recommendations are unlikely to be effective unless accompanied by the necessary **policy changes**, which are not all covered in these guidelines. Based on expert opinion the Guideline Development Group made a number of health system recommendations, also printed on pages 146 and 147. More comprehensively, all recommendations and their background are discussed throughout this publication. However, for a comprehensive overview of legal and policy issues to address, reference is made to the WHO policy guidelines *Ensuring balance in national policies on controlled medicines: guidance for availability and accessibility of controlled medicines (95).*

Future research

In the course of the development of these guidelines, the gaps in research on pharmacological interventions in neonates, infants and children have been noted and mapped. The majority of the studies considered in these guidelines have been conducted in children with acute pain and do not appropriately address research questions regarding children requiring long-term pain treatment.

Therefore, the Guideline Development Group calls upon the scientific community to invest in clinical research on the safety and efficacy of pain-relieving medicines specifically in children with persisting pain due to medical illnesses. Any outcomes measured in clinical studies comparing different pharmacological interventions should include both positive (efficacy, quality of life etc.) and negative (prevalence and severity of adverse effects etc.) outcomes.

The Guideline Development Committee has prioritized a list of research questions/areas as follows:

First group of priorities

- Assessment of two-step treatment strategy.
- Research on alternative strong opioids to morphine (comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use).
- Research on intermediate potency opioid analgesics (e.g. tramadol).
- Long-term safety data concerning first-step medicines (ibuprofen/paracetamol).

Second group of priorities (neuropathic pain)

- Antidepressants, specifically tricyclic antidepressants and selective serotonin reuptake inhibitors and newer antidepressants of the class of serotonin and norepinephrine reuptake inhibitors for persisting neuropathic pain in children.

- Gabapentin for persisting neuropathic pain in children.
- Ketamine as an adjuvant to opioids for refractory neuropathic pain in paediatric patients with long-term medical illness.

Third group of priorities
- Randomized controlled trials (RCTs) on alternative routes to the oral route of opioid administration (including RCTs comparing subcutaneous and intravenous routes).

Fourth group of priorities
- Update Cochrane reviews on opioid switching including paediatric data, if available.
- Randomized controlled trials on opioid switching and research on dose conversion in different age groups.
- Randomized controlled trials on short-acting opioids for breakthrough pain in children.

Other areas for research and development
- Research and psychometric validation of observational behaviour measurement tools for persisting pain settings (neonates, infants, preverbal and cognitively impaired children).
- Prospective clinical trials to investigate opioid rotation protocols and their efficacy in preventing side-effects or opioid tolerance and dose escalation.
- Development of divisible, dispersible, oral solid-dosage forms of paracetamol and ibuprofen.
- Research into appropriate formulations for the extemporaneous preparation of oral liquid morphine. Dissemination of available evidence on the preparation of stable extemporaneous formulations.
- Child-appropriate oral solid dosage forms of opioid analgesics.
- Research on equianalgesic dosages in conversion of opioid analgesics for different age groups.

Reading guide

The *Introduction* explains the objective of these guidelines, with a description of their scope, including which types of pain are specifically included and excluded. It also describes the patients to which they apply and the audience for whom the guidelines were developed.

Chapter 1. *Classification of pain in children* provides a description of pain classification systems.

Chapter 2. *Evaluation of persisting pain in the paediatric population* gives general guidance and key concepts on the assessment and evaluation of pain in children.

Chapter 3. *Pharmacological treatment strategies* provides clinical guidance to health professionals. It presents the recommendations for pharmacological interventions. Moderate and severe pain in children should always be addressed. The main pharmacological recommendation for the treatment of children affected by persisting pain caused by cancer, major infections (such as HIV/AIDS), sickle cell disease, burns, trauma and neuropathic pain following amputation, foresees treatment with a two-step approach based on the severity of pain. Paracetamol or ibuprofen are the medicines of choice in the first step and are used for treatment of mild pain. Morphine, as a strong opioid, is the medicine of choice in the second step and is used for treatment of moderate to severe pain. Both strong opioids and non-opioid analgesics should always be available at all levels of health care. With the publication of these guidelines, WHO's "three-step analgesic ladder for cancer pain relief" has been abandoned for children *(21).*

Chapter 4. *Improving access to pain relief in health systems* provides considerations of how to improve access to pain treatment and includes four policy recommendations.

Pharmacological profiles for selected medicines appear in **Annex 1.** *Pharmacological profiles.*

Annex 2. *Background to the clinical recommendations* describes the development process of this document, the considerations included by the Guidelines Development Group when formulating the recommendations, and a brief statement of non-pharmacological interventions.

Annex 3. *Background to the health system recommendations* provides the considerations of the Guidelines Development Group when formulating the recommendations from Chapter 4.

Annex 4. *Evidence retrieval and appraisal* presents the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables developed using the retrieved literature, the studies retrieved on health system recommendations, as well as the observational studies retrieved on topics for which there were no systematic reviews and randomized clinical trials.

Since many issues could not be completely resolved because of the lack of current research, **Annex 5.** *Research agenda* was developed.

International requirements for the handling and procurement of morphine and other opioid analgesics for the relief of pain are described in **Annex 6.**

Finally, **Annex 7** lists all those who contributed to these guidelines.

A **Summary** of all principles and recommendations presented in this guidelines document, the **Reference List** and the **Index** are presented at the end of this book.

INTRODUCTION

The overall objective of these guidelines is to provide evidence-based recommendations on pain treatment, including opioid analgesics, non-opioid analgesics and adjuvant medicines to improve the management of pain in children, that is, neonates, infants and children aged 0-10 years experiencing persisting pain related to medical diseases. They can also be applied to adolescents as the majority of the evidence retrieved and appraised refers to studies in populations comprising patients from 0 to 18 years.

The guidelines deal specifically with the **pharmacological management of persisting pain in children with medical illnesses**, where "persisting pain" refers to any long-term pain and "medical illnesses" refers to specific situations of ongoing tissue damage where there is a clear role for pharmacological treatment.

Types of pain **included** are nociceptive pain due to inflammation or tissue injury, as well as neuropathic pain from nerve compression or disruption, resulting from disease. Conditions considered include but are not restricted to persisting pain from cancer, cancer treatment, major infection (e.g. HIV/AIDS), arthritis and other rheumatological diseases, sickle cell disease (SCD), trauma, burns, persisting neuropathic pain following amputation, etc.

These guidelines **exclude** acute traumas, perioperative and procedural pain. Also, chronic complex pain where there is no evidence of ongoing tissue disruption such as fibromyalgia, headache, or recurrent abdominal pain is not addressed, as treatment of these conditions requires a multimodal approach with extensive use of non-pharmacological techniques as well as pharmacological therapy. Non-pharmacological interventions such as cognitive-behavioural therapy, other psychological techniques and physical interventions are important, often effective and are elements of an integrated pain management plan. However, review and recommendations regarding these techniques are also beyond the scope of these guidelines.

Furthermore, disease-specific therapies, such as anti-cancer and sickle cell disease therapies, are an essential component of care, but fall outside the scope of these guidelines.

The **targeted audience** for these guidelines are health-care providers in the widest meaning: from medical practitioners, clinical officers, nurses and pharmacists, to personnel caring for children. They are also intended for policy-makers and public-health and programme managers, who may not be directly involved in providing care for children, but nevertheless play a crucial role in making rapid, effective and safe pain management available at various levels of the health system. Policy-makers and regulatory authorities are crucial in facilitating legal access to – and ensuring proper use of – opioid analgesics for pain management.

These guidelines will also provide the basis for a number of other WHO publications related to the management of moderate to severe pain in children for specific audiences. They may be intended specifically for palliative-care workers, for pharmacists, or for policy-makers and hospital directors. They may also include agenda cards with dosing tables and wall charts for addressing the patients and their caregivers. Furthermore, the recommendations in these guidelines will be used to update other WHO documents pertinent to child health guidance.

An update of these guidelines should ideally take place within four to five years. However, given the considerable resources that have been invested in the guidelines development process and the paucity of studies in the field of persisting pain in the paediatric population, a meaningful update may not be possible without action on the research agenda annexed to these guidelines.

The development process followed for these guidelines is described in Section A2.1 of Annex 2, followed by the background for all clinical recommendations. The background for the health policy recommendations is provided in Annex 3. Essentially, the recommendations are divided into two levels of strength, "strong" or "weak" and should be interpreted by patients, clinicians and policy-makers as outlined in Box 0.2.

Box 0.1 Definition of quality of evidence according to GRADE

- *High*: further research is unlikely to change confidence in the estimates of the effect.
- *Moderate*: further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate.
- *Low*: further research is very likely to have an important impact on the confidence of the effect and is likely to change the estimate.
- *Very low*: any estimate of effect is very uncertain.

Box 0.2 Interpretation of strong and weak recommendations

Strong recommendations may be interpreted as follows:

- patients: most patients would want the recommended course of action and only a small proportion would not;
- clinicians: most patients should receive the recommended course of action and adherence to this recommendation is a measure of good quality care;
- policy-makers: the recommendation can be adopted as a policy in most situations and should unequivocally be used for policy-making.

Weak recommendations may be interpreted as follows:

- patients: the majority of patients in this situation would want the recommended course of action, but many would not;
- clinicians: help patients to make a decision that is consistent with their own values;
- policy-makers: there is need for substantial debate and involvement of stakeholders.

The pharmacological profiles of the medicines recommended as a first choice were extracted from the *WHO model formulary for children* (*1*) and adapted for use in children with persisting pain due to medical illnesses. Similarly, the pharmacological profiles of opioid analgesics for safe opioid switching were compiled following the same methods used by the *WHO model formulary for children.*

The recommendations formulated on health-system issues are based on published and unpublished experience in the management of pain in health systems, and the implementation and quality of care provided for other medical conditions (Chapter 4, *Improving access to pain relief in health systems*, and Annex 3, *Background to the health system recommendations*). These recommendations are based on the Guidelines Development Group experts' opinion.

Prior to describing the pharmacological treatment of pain in Chapter 3, an introduction to types of pain and their relevance for treatment (Chapter 1) and an introduction to assessment of pain in children (Chapter 2) are presented. In particular, good assessment of pain is essential for the appropriate treatment of pain.

Potential conflicts of interest and their management are mentioned in Annex 7, *List of contributors to this publication.*

1 CLASSIFICATION OF PAIN IN CHILDREN

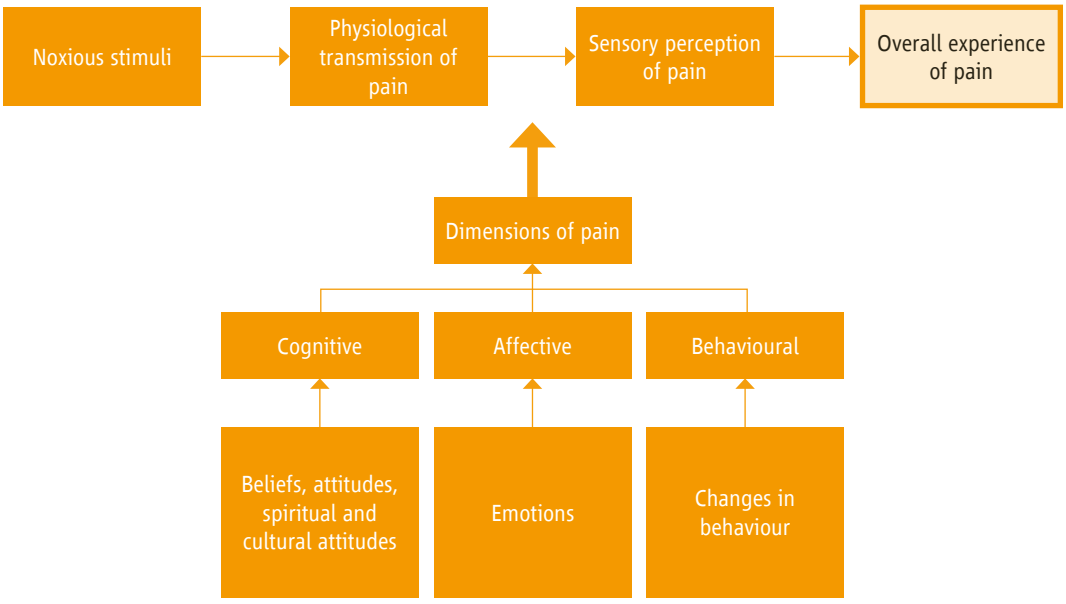
This chapter presents and explains four of the more commonly used classification systems of pain. Several classification systems exist but no international classification system has been unanimously adopted. This chapter permits discrimination among the different terms used to categorize pain and the classification system to which each belongs. It also defines which classification system is relevant to the clinical management of pain and describes the most common causes of pain in HIV/AIDS, cancer and sickle cell disease.

1.1 Introduction to classification of pain

The International Association for the Study of Pain (IASP) defines pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (*2*). The definition emphasizes both the physical and emotional nature of pain. An additional note is pertinent to pain experienced by children: "The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective ...." (*3*).

Pain is a multidimensional phenomenon with sensory, physiological, cognitive, affective, behavioural and spiritual components. Emotions (affective component), behavioural responses to pain (behavioural component), beliefs, attitudes, spiritual and cultural attitudes about pain and pain control (cognitive component) all alter the way that pain is experienced (sensory component) by modifying the transmission of noxious (unpleasant) stimuli to the brain (physiological component) (Figure 1.1).

Figure 1.1 Diagram showing the many dimensions of pain modifying the transmission of noxious stimuli to the brain



The four **most commonly used systems** are (*4, 5*):

- the pathophysiological mechanism of pain (nociceptive or neuropathic pain);
- the duration of pain (chronic or acute, breakthrough pain);
- the etiology (malignant or non-malignant);
- the anatomic location of pain.

Some causes of persisting pain in children may result from (*6*):

1. **chronic diseases** such as arthritis, sickle cell disease and rheumatologic disorders constitute important causes of musculoskeletal pain and chronic conditions such as inflammatory bowel disease can cause recurrent abdominal pain.
2. **trauma – physical, thermal, electrical and chemical injuries** (e.g. burns) and lead to, for instance, phantom limb pain or lower back pain.
3. **life threatening diseases** and their treatment such as simultaneous acute and chronic pain in cancer and HIV/AIDS.

Idiopathic pain has no identifiable etiology. Examples are most headaches and recurrent abdominal pain.[1]

Pain in specific disease conditions, such as cancer, HIV/AIDS and sickle cell disease, can be classified as mixed acute and/or chronic and may arise due to many of the causes discussed in Section 1.3.

1.2 Pain classification systems

1.2.1 Pathophysiological classification

There are two major types of pain, nociceptive and neuropathic. Clinical distinction between nociceptive and neuropathic pain is useful because the treatment approaches are different.

Nociceptive pain arises when tissue injury activates specific pain receptors called nociceptors, which are sensitive to noxious stimuli. Nociceptors can respond to heat, cold, vibration, stretch stimuli and chemical substances released from tissues in response to oxygen deprivation, tissue disruption or inflammation. This type of pain can be subdivided into *somatic* and *visceral* pain depending on the location of activated nociceptors.

- ***Somatic pain*** is caused by the activation of nociceptors in either surface tissues (skin, mucosa of mouth, nose, urethra, anus, etc.) or deep tissues such as bone, joint, muscle or connective tissue. For example, cuts and sprains causing tissue disruption produce surface somatic pain while muscle cramps due to poor oxygen supply produce deep somatic pain.
- ***Visceral pain*** is caused by the activation of nociceptors located in the viscera (the internal organs of the body that are enclosed within a cavity, such as thoracic and abdominal organs). It can occur due to infection, distension from fluid or gas, stretching or compression, usually from solid tumours.

Neuropathic pain is caused by structural damage and nerve cell dysfunction in the peripheral or central nervous system (CNS) (*7*). Any process that causes damage to the nerves, such as metabolic, traumatic, infectious, ischaemic, toxic or immune-mediated pathological conditions, can result in neuropathic pain. In addition, neuropathic pain can be caused by nerve compression or the abnormal processing of pain signals by the brain and spinal cord.

[1] *Several types of headaches can affect children including migraine, tension, and cluster headaches.*

Neuropathic pain can be either *peripheral* (arising as a direct consequence of a lesion or disease affecting the peripheral nerve, the dorsal root ganglion or dorsal root) or *central* (arising as a direct consequence of a lesion or disease affecting the CNS). However, a clear distinction is not always possible.

Neuropathic pain has rarely been studied in infants, children and adolescents. Causes of peripheral neuropathic pain in children include nerve injury, nerve entrapment or external compression by any space-occupying lesion, such as a tumour or abscess; nerve damage caused by HIV infection or by the toxic effects of antiretroviral therapy (ART); benign tumours of the nerve, such as neurofibroma or scar neuroma after trauma or surgery; phantom limb pain; nerve infiltration by cancers; and nerve damage caused by cancer treatment (e.g. chemotherapy, radiation). Causes of central neuropathic pain include pain due to spinal cord injury. Furthermore, children can be affected by other neuropathic pain syndromes, such as congenital degenerative peripheral neuropathies and inflammatory neuropathies (e.g. Guillain-Barré syndrome) *(8, 9)*. Many of the neuropathic conditions commonly seen in adults, such as diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia, are rare in children.

Neuropathic pain is associated with many types of sensory dysfunction which are defined in Table 1.1.

Table 1.1 Common sensory features suggestive of neuropathic pain

Sensory dysfunction	Definition
Allodynia	Pain due to a stimulus that normally does not provoke pain. For example, a light touch may elicit severe pain.
Hyperalgesia	Increased pain response to a normally painful stimulus (tactile or thermal, both are rare). Hyperalgesia to cold occurs more frequently than to heat.
Hypoalgesia	Diminished pain response to a normally painful stimulus (tactile or thermal, both are frequent).
Paraesthesia	Abnormal sensation to a stimulus that is normally not unpleasant such as tingling, pricking or numbness. It may be spontaneous or evoked.
Dysesthesia	Unpleasant sensation. It may be spontaneous or evoked.
Hyperesthesia	Increased sensitivity to stimulation (tactile or thermal, both are rare).
Hypoesthesia	Decreased sensitivity to stimulation (tactile or thermal, both are frequent).

Source: (*7*)

Mixed pain. Neuropathic pain may coexist with nociceptive pain. In some disease conditions, patients may have mixed pain consisting of somatic, visceral and neuropathic pain all at the same time or each separately at different times. The different pathophysiological mechanisms described above can operate together to produce mixed pain. Examples include trauma that damages tissue and nerves, burns (that affect skin as well as nerve endings), and cancer that causes external nerve compression as well as damaging nerves by infiltration.

Clinical distinction between nociceptive and neuropathic pain is based on the anatomic origin of the stimulus, whether it is well-localized or diffuse, and the character of the pain (e.g. sharp, dull, burning) as described in Table 1.2.

In some types of painful conditions, the pathophysiological mechanisms of pain are not well understood and/or cannot be demonstrated. Such pain is often wrongly labelled as psychogenic. While psychological factors are known to influence the perception of pain, true psychogenic pain is very rare. Limitations in our current knowledge and diagnostic testing may also be the reasons for the inability to find any underlying cause and it is, therefore, recommended that the term **idiopathic** be used instead (*10*), thereby keeping open the possibility of diagnosing an organic process, which may reveal itself at a later stage or when more sensitive diagnostic tools become available.

If no physical pathology is found on clinical examination, laboratory tests and imaging studies, it is more effective to focus on rehabilitation and restoration of function than on repeated investigations.

All patients with pain should be treated with either pharmacological or non-pharmacological techniques irrespective of whether or not the underlying cause can be identified. Inability to establish an underlying cause should not be a reason to conclude that the pain is simulated.

1.2.2 Classification based on pain duration

A commonly used definition of *acute* pain is pain lasting less than 30 days, and a commonly used definition of *chronic* pain is pain lasting more then three months. However, these definitions are arbitrary and not essential for deciding on treatment strategies. Symptoms and causes of the two types of pain may overlap and pathophysiological factors can be independent of duration. Therefore, this division between acute and chronic pain based on duration may be problematic.

Acute pain is of sudden onset, is felt immediately following injury, is severe in intensity, but is usually short-lasting (*4*). It arises as a result of tissue injury stimulating nociceptors and generally disappears when the injury heals.

Chronic pain is continuous or recurrent pain that persists beyond the expected normal time of healing (*3*). Chronic pain may begin as acute pain and persist for long periods or may recur due to persistence of noxious stimuli or repeated exacerbation of an injury. Chronic pain may also arise and persist in the absence of identifiable pathophysiology or medical illness. Chronic pain can negatively affect all aspects of daily life, including physical activities, school attendance, sleep patterns, family interactions and social relationships and can lead to distress, anxiety, depression, insomnia, fatigue or mood changes, such as irritability and negative coping behaviour. As pain is an outcome of an interaction of many factors, the child as a whole must be considered when evaluating the clinical features of pain. Therefore, a holistic approach may be required to relieve pain.

Episodic or recurrent pain occurs intermittently over a long period of time and the child can be pain free in between each painful episode. Painful episodes can often fluctuate in intensity, quality and frequency over time and are consequently unpredictable. This type of pain may be indistinguishable from recurrent acute pain but might be associated with a more severe impact on the affected child's physical and psychosocial life. Examples of this type of pain include migraine, episodic sickle cell disease pain, recurrent abdominal pain. Persisting and recurrent pain can coexist, especially in conditions such as in sickle cell disease.

Breakthrough pain is characterized as a temporary increase in the severity of pain over and above the pre-existing baseline pain level, e.g. if a child is taking pain medicines and has good pain control with a stable analgesic regimen and suddenly develops acute exacerbation of pain. It is usually of sudden onset, severe, and of short duration. A number of episodes of breakthrough pain can occur each day. It is a well-known feature in cancer pain but it is also seen in non-malignant pain conditions (*11, 12*). Breakthrough pain can occur unexpectedly and independently of any stimulus, i.e. without a preceding incident or an obvious precipitating factor.

Incident pain or pain due to movement has an identifiable cause. The pain can be induced by simple movements, such as walking, or by physical movements that exacerbate pain, such as weight bearing, coughing or urination. Diagnostic or therapeutic procedures can also cause incident pain.

End of dose pain results when the blood level of the medicine falls below the minimum effective analgesic level towards the end of dosing interval.

The term "persisting pain" as used in these guidelines is intended to cover long-term pain related to medical illness, for example, pain associated with major infections (e.g. HIV), cancer, chronic neuropathic pain (e.g. following amputation), and episodic pain as in sickle cell crisis.

1.2.3 Etiological classification

Classification by etiology has little relevance to the mechanism and treatment of pain in children as categorization is commonly based on the underlying disease being *malignant* or *non-malignant*.

1.2.4 Anatomical classification

Pain is often classified by body location (e.g. head, back or neck) or the anatomic function of the affected tissue (e.g. myofascial, rheumatic, skeletal, neurological and vascular). However, location and function solely address the physical dimension and do not include the underlying mechanism (*13*). As such, although anatomical classifications can be useful for differential diagnoses, these classifications do not offer a framework for clinical management of pain.

Table 1.2 Differentiating features of nociceptive and neuropathic pain

Type of pain	Origin of stimulus	Localization	Character	Referral and radiation of pain/sensory dysfunction	Examples
Nociceptive pain Superficial somatic pain	Arises from nociceptors in skin, mucosa of mouth, nose, urethra, anus, etc. Nociceptive stimulus is evident.	Well localized	Usually sharp and may have a burning or pricking quality.	None	• abscesses • postsurgical pain from a surgical incision • superficial trauma • superficial burn
Nociceptive pain Deep somatic pain	Arises from nociceptors in bone, joint, muscle and connective tissue. Nociceptive stimulus is evident.	Usually well localized with tenderness to palpation.	Usually dull or aching or throbbing in quality.	In some instances, pain is referred to the overlying skin. No associated sensory dysfunction.	• bone pain due to metastasis • fractures • muscle cramps • sickle cell vaso-occlusive episodes
Nociceptive pain Visceral pain	Arises from nociceptors in internal organs such as the liver, pancreas, pleura and peritoneum.	Poorly localized, diffused. Palpation over the site may elicit an accompanying somatic pain.	Usually vague, dull, aching, cramping or tightness, deep pressure, spasms, or squeezing or colicky in nature. Nausea, diaphoresis and emesis are frequently present.	In some instances, pain referred to skin supplied by same sensory roots that supply the diseased organ. There may be radiation of the visceral pain, but it will not be in a direct nerve distribution. No associated sensory dysfunction.	• pain from acid indigestion or constipation • pain due to stretching from liver metastasis, pleura stretching due to pleuritis, as in pneumonia or tuberculosis
Neuropathic pain	Is generated at various sites, and is not always stimulus-dependent.	Poorly localized, diffuse pain in an area of sensory dysfunction in the area of anatomical distribution of nerve supply.	Difficult to describe and different words may be used in different populations: • burning, pricking or needle like pain; • sharp or shooting. The pain may be persisting or recurrent.	Neuropathic pain is perceived within the innervation territory of the damaged nerve. There may be abnormal radiation. The pain is associated with sensory dysfunction (dysesthesia, hypoesthesia, hyperesthesia and allodynia).	• central neuropathic pain due to spinal cord injury from trauma or tumour • painful peripheral neuropathies, due to HIV/AIDS, cancer or anti-cancer treatment pain (e.g. chemotherapy with vincristine) • phantom limb pain

Sources: adapted from *(7, 8, 14, 15).*

1.3 Causes and classification of pain associated with specific diseases

1.3.1 Causes and types of pain in children with HIV/AIDS

Common types of pain experienced by infants with HIV include headache, oral cavity pain, abdominal pain, neuromuscular pain, chest pain, earache, odynophagia (pain while swallowing), myalgia and arthralgia (*16, 17*). In older children, the type of pain is often a function of the clinical stage of the infection. In early HIV, most pain occurs as a result of opportunistic conditions and is, therefore, somatic and transient in nature. During the later stages of the disease, somatic pain still occurs, but neuropathic pain, e.g. pain caused by peripheral neuropathy and myelopathy, is also seen.

The World Health Organization has provided paediatric clinical staging criteria for children infected with HIV. There are four clinical stages based on clinical symptoms, which may be used to guide medical decision-making (*18*):

- Stage I: asymptomatic or persistent generalized lymphadenopathy;
- Stage II: mucocutaneous manifestations, herpes zoster, and recurrent upper respiratory tract infections;
- Stage III: unexplained persistent diarrhoea, unexplained persistent fever, oral candida, lymph node tuberculosis, pulmonary tuberculosis, and severe bacterial infection (e.g. pneumonia);
- Stage IV: unexplained severe wasting or severe malnutrition, recurrent severe bacterial infections, and extrapulmonary tuberculosis.

Children with HIV/AIDS experience pain throughout the course of the disease. Disease-related pain can result from both infectious and non-infectious pathological conditions and can be acute or chronic. Pain associated with opportunistic infections (i.e. pneumonia, meningitis, gastroenteritis) should be considered, as should pain management for any procedures. In addition, the selection of therapeutic options must take into account the challenges associated with drug interactions. Below is a summary of types of pain seen in patients with HIV/AIDS characterized by location-associated symptoms and etiology (*16, 19*).

Causes of acute pain in HIV/AIDS

- *Oral cavity pain:* aphthous ulcers, oral infections due to candida (white patches or red sores), herpes (cold sores), and cytomegalovirus may cause dysphagia, and pain which can be located on the tongue, gums, lips or roof of the mouth. There may be associated diarrhoea and vomiting. Oral cavity pain in turn leads to poor oral intake, increased weight loss, malnutrition, failure to thrive and progression to wasting syndrome (described below). In advanced cases of candidiasis, infection may extend into the oesophagus causing pain, especially when swallowing.
- *Abdominal pain* can be caused by intestinal infections, urinary tract infection, pancreatitis, hepatitis and colitis. Diarrhoea and vomiting are commonly associated with abdominal pain. Cramping or episodic pain is often seen in settings where there is intestinal infection or bowel obstruction (e.g. secondary to inflammation). Children with HIV can also develop abdominal sepsis and present with an acute abdomen where pain is continuous, severe and exacerbated by movement.
- *Headache* can be due to sinusitis, meningitis or encephalitis. Children with HIV can also experience non-infectious causes of headache such as tension headache and migraine. Infections of the central nervous system may give rise to fever, epileptic seizures as well as variability in consciousness along with pain.

- *Neurological and neuromuscular pain* is common in the setting of static and progressive encephalopathy, especially when there is hypertonicity, spasticity and muscular spasms. Myopathy and herpes zoster are other important causes of neurological or neuromuscular pain.
- *Ear pain* can occur due to infections of the middle ear (otitis media) or of the ear canal (otitis externa).
- *Skin pain caused by sores and rashes* can occur due to infections (viral, bacterial or fungal). It can be both acute and chronic. Chickenpox and herpes simplex cause blisters that can hurt and itch. Skin pain may also be caused by acute cellulitis.
- *Chest pain*: pneumonia and pulmonary tuberculosis accompanied by severe respiratory distress and coughing may cause both pain and distress.
- *Generalized pain*: some children with HIV complain about generalized pain without any localizing site. Usually this type of pain is seen in very sick children.
- *Side-effects of antiretroviral therapy (ART)* such as diarrhoea may induce painful complications such as diaper dermatitis. Medicine-specific side-effects include muscle pain (zidovudine), headache (efavirenz) and abdominal pain (stavudine).

Causes of persisting pain in HIV/AIDS

- *Neuropathic pain:* peripheral neuropathy due to damage to the nerves by HIV and the adverse effect of ART described as discomfort, burning or numbness. In particular, nucleoside reverse transcriptase inhibitors – especially stavudine and didanosine – are associated with neuropathy (*20*). Herpes zoster infection may cause severe pain after the sores have healed, due to neuropathy (post-herpetic neuralgia).
- *Wasting syndrome* can be associated with chronic diarrhoea (contributing to buttock ulceration and cramping), mouth and throat ulceration, fatigue, fever and weakness (enhancing any pain experience), depression, musculoskeletal pain, abdominal pain, and neuropathy secondary to nutritional deficiencies.

1.3.2 Causes and types of pain in children with cancer

In developed countries, most cancer pain in children is related to diagnostic and therapeutic procedures and treatment. Tumour-related pain often occurs at diagnosis, particularly when disease recurs and also occurs when the child's cancer is resistant to treatment. In developing countries, where large numbers of children with cancer present at an advanced stage and few have access to chemotherapy or radiotherapy, cancer pain is usually due to progression of the cancer itself (*21*).

The cancer mass can produce pain by tissue distension, compression or infiltration. Inflammation due to infection, necrosis or obstruction can also cause pain. The classification of cancer pain presents a unique challenge due to the complexity of the cancer pain in terms of variety of pathophysiological mechanisms and pain syndromes, and the need to provide information on prognosis and treatment outcomes. Disease-related pain in cancer can be acute or chronic (*21–23*).

Causes of acute pain in children with cancer

Acute cancer pain can be caused by direct invasion of anatomical structures by the tumour, resulting in pain through pressure, distension, inflammation, obstruction and nervous tissue compression. Acute pain also occurs in relation to investigative or therapeutic procedures, such as bone-marrow aspiration and lumbar puncture. Incidental pain from unrelated causes or concomitant disease may also occur in children with cancer. Metastatic spinal cord compression may be a cause of acute back pain and metastatic brain tumour can cause severe headaches. Mucositis after chemotherapy or radiotherapy is also a frequent cause of pain in children with cancer.

Causes of persisting pain in children with cancer

Chronic pain can be either caused by the tumour growth itself or by various cancer-related diagnostic and therapeutic procedures, such as limb amputation or chemotherapy. The common childhood malignancies, such as leukaemia, lymphoma, bone sarcomas and neuroblastoma, can cause diffuse bone and joint pain. Leukaemia, brain tumours and lymphomas can cause headache. *Neuropathic pain* is caused by injury to the nervous system either as a result of a tumour compressing or infiltrating nerves or the spinal cord, or by damage caused by the treatment (chemotherapy, radiation). This type of pain is often severe and usually described as burning, tingling, sharp or shooting.

1.3.3 Causes and types of pain in children with sickle cell disease

Sickle cell disease (SCD) is a common genetic disorder characterized by the presence of abnormal haemoglobin (haemoglobin S) in the red blood cells. The term "sickle cell disease" is generally used to describe all conditions associated with the phenomenon of red blood cell sickling, whereas the term "sickle cell anaemia" is generally used to describe homozygosity for haemoglobin S (HbS). Apart from the latter, the disorder may result from different other genetic conditions, including compound heterozygosity for HbS and an abnormal haemoglobin (e.g. sickle cell haemoglobin) or HbS/beta-thalassaemia. All these conditions may have varying degrees of severity depending on the underlying genetic defect and interacting genetic factors. Individuals who are heterozygous for HbS (sickle cell trait) are usually asymptomatic. The presence of HbS causes red blood cells to become rigid and crescent shaped (i.e. sickled). When large numbers of sickled red blood cells collect, they hinder blood flow, which results in painful vaso-occlusive crises or episodes. The resultant ischaemia leads to tissue damage and cell necrosis, which cause nociceptive pain. Pain may originate from many sources (e.g. musculoskeletal and visceral) and children and adolescents experience both persisting and episodic pain (often defined as acute pain) (*24, 25*).

Episodic (acute) SCD pain occurs due to acute vaso-occlusive episodes ("sickle cell crises"). The arms, legs, abdomen, chest and back are the most common locations of pain episodes. Children describe pain associated with SCD as aching, tiring and uncomfortable. Children with SCD may experience pain as early as 6–12 months of age. On average painful episodes persist for four or five days, although protracted episodes may last up to three weeks. One of the more debilitating aspects of vaso-occlusive episodes is their unpredictable nature in terms of frequency, intensity, affected sites and duration of pain (*25*). It is thought that vaso-occlusive episodes are triggered by various environmental and psychological states, such as high altitudes, extreme temperatures, infection, dehydration, stress and fatigue (*26*). Painful episodes experienced by children with SCD often interfere with intellectual activities, such as attending school and completing homework; social activities, such as participating in activities with family members and peers; and the quality and quantity of sleep.

Persisting SCD pain is more common in adults than in children and more common in adolescents than in young children. Avascular necrosis due to poor blood oxygenation can cause chronic pain in limbs and joints. Poor circulation can lead to chronic leg ulcers. In addition, vertebral collapse can be the source of chronic back pain. As chronic pain increases in frequency and severity in a child with SCD, a cycle of inadequate coping skills, poor relationships, and worsening pain may sometimes develop (*27*).

2 EVALUATION OF PERSISTING PAIN IN THE PAEDIATRIC POPULATION

Optimal pain management begins with accurate and thorough pain assessment. Pain assessment enables health-care providers to treat pain and alleviate needless suffering. It should be carried out at regular intervals because the disease process and the factors that influence it may change over time and regular assessment permits the measurement of the efficacy of different treatment strategies in relieving pain. The pain assessment process involves the child, the parents or caregivers and the health-care providers.

Pain assessment should be integrated into all clinical care. The way a child perceives pain is an outcome of biological, psychological, social, cultural and spiritual factors. Therefore, a comprehensive approach to pain assessment is required.

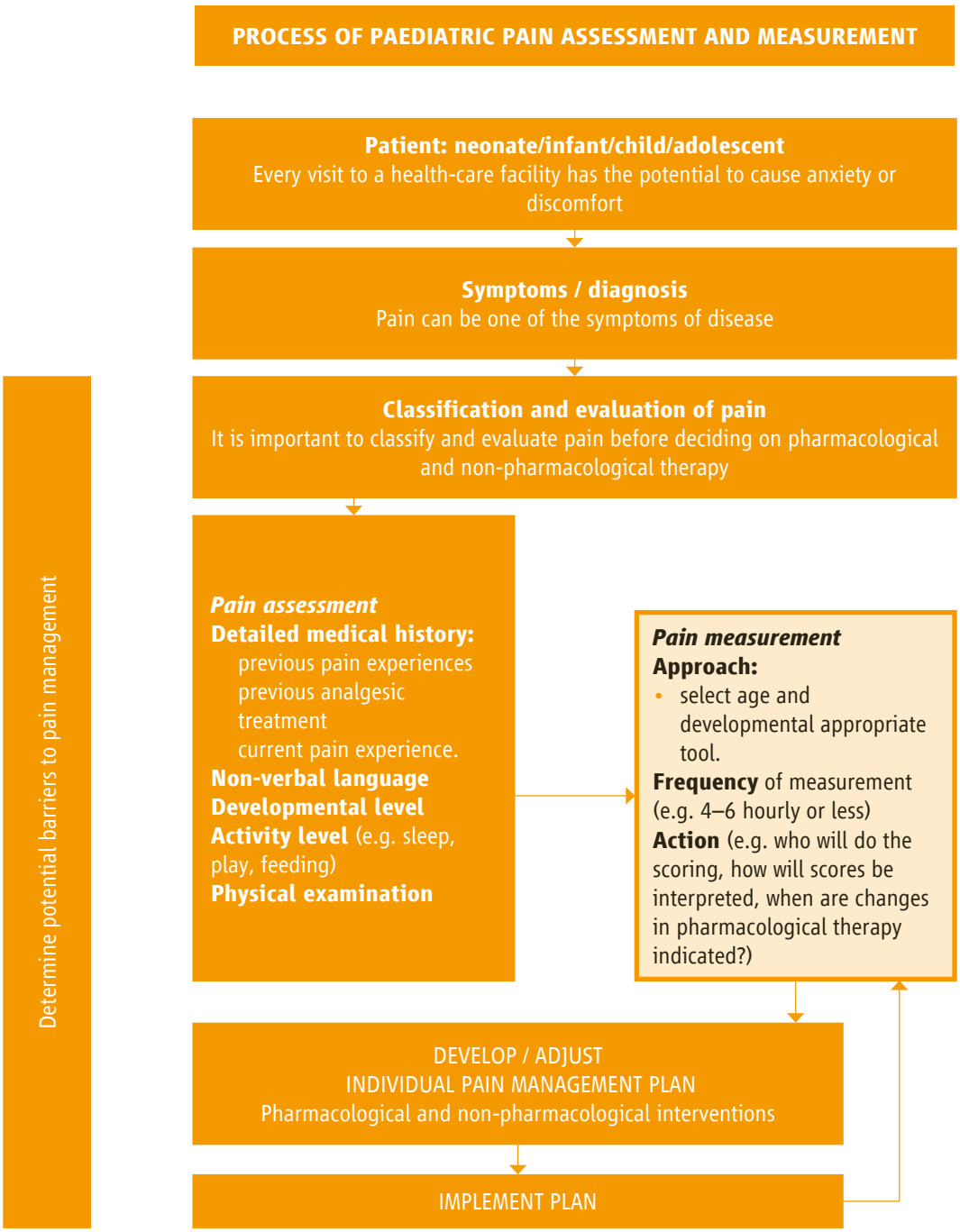
2.1 Clinical examination: pain history and physical examination

The initial pain assessment of a child reporting or presenting behavioural signs of pain includes a detailed pain history, a physical examination, the diagnosis of the causes, and the measurement of pain severity using an age-appropriate pain measurement tool. Pain assessment involves obtaining information about the location, duration and characteristics of the pain, as well as the impact of persisting pain on various aspects of the child's life such as sleep, emotional state, relationships, development and physical function (*28*) (See Box 2.1, below). The health-care provider should try to investigate the pain's association with any triggering factors by asking about any known aggravating and relieving factors. The health-care provider should ask what pain management treatments have previously been used, as well as the efficacy of any treatments.

Following this assessment, a detailed pain management plan, including pharmacological and non-pharmacological interventions, can be formulated and implemented together with the child's primary caregiver. Pain measurement should be performed at regular intervals during the implementation of the pain management plan. This permits the measurement of changes in the severity of pain over time, and the assessment of the adequacy and efficacy of the chosen treatment, and enables adjustments to be made, as necessary. The algorithm in Figure 2.1 describes these elements and their relationship to each other.

The process should include an assessment of the child's cognitive developmental level and information on the usual behaviour of the child when he or she is not experiencing pain. Assessment may be problematic in preverbal children and children who are physically underdeveloped due to malnutrition and illnesses.

Figure 2.1 Algorithm on evaluation of pain in the paediatric population



Box 2.1 Summary of questions by the health-care provider during clinical evaluation

- What words do the child and family use for pain?
- What verbal and behavioural cues does the child use to express pain?
- What do the parents and/or caregivers do when the child has pain?
- What do the parents and/or caregivers not do when the child has pain?
- What works best in relieving the pain?
- Where is the pain and what are the characteristics (site, severity, character of pain as described by the child/parent, e.g. sharp, burning, aching, stabbing, shooting, throbbing)?
- How did the present pain start (was it sudden/gradual)?
- How long has the pain been present (duration since onset)?
- Where is the pain (single/multiple sites)?
- Is the pain disturbing the child's sleep/emotional state?
- Is the pain restricting the child's ability to perform normal physical activities (sit, stand, walk, run)?
- Is the pain restricting the child's ability/willingness to interact with others, and ability to play?

A thorough physical examination is essential and each location of pain should be carefully evaluated. During the examination, the examiner should watch carefully for any reactions from the child, such as facial grimacing, abdominal rigidity, involuntary flexion, and verbal cues, which may indicate pain. Any change in normal physical function caused by pain should be assessed.

The information gathered from the history and physical examination will help to identify a differential diagnosis of the cause(s) of pain, and can guide for the choice of laboratory and radiological investigations to confirm diagnosis, if not yet established.

2.2 Expression of pain by children and appropriate pain assessment measures

Pain expression is dependent on the child's age, cognitive development, and sociocultural context and it is important to pay particular attention to developmental variations in any behavioural manifestations of pain.

Young children usually use the simple words that they learn from their parents to express pain (such as "ouch") and may point to the part of their body in which they feel the pain. The ability to indicate the presence of pain verbally emerges between two and four years old. Gradually they learn to distinguish three levels of pain such as "a little", "some", and "a lot". By five years old, children can describe pain and define its intensity. At six years old, they can clearly differentiate the levels of pain intensity. Children from seven to ten years of age can explain why it hurts (*29*).

In children unable to talk, pain reporting is reliant on parents and/or caregivers (*30, 31*). Parents usually know their child's typical behavioural response to pain and this can be included in the pain assessment. **Observation of behaviour** in relation to pain is a valid approach for pain assessment in children below three years old, and in children with limited verbal and cognitive skills. Such behavioural responses may vary depending on whether the pain is acute or persisting.

The main **behavioural indicators of acute pain** are:

- facial expression
- body movement and body posture
- inability to be consoled
- crying
- groaning.

These behavioural responses may be reduced in persisting pain, except during acute exacerbation. **Behaviour in children with chronic pain** can include (*32*):

- abnormal posturing
- fear of being moved
- lack of facial expression
- lack of interest in surroundings
- undue quietness
- increased irritability
- low mood
- sleep disruption
- anger
- changes in appetite
- poor school performance.

However, children may display none of the expected cues. They may deny their pain for fear of more painful treatment, for example, they may be fearful of injections. Absence of these signs does not mean absence of pain and care should be taken to avoid underestimating pain.

Caregivers are often the primary source of information, especially **for preverbal children,** as they are best aware of the child's previous pain experiences and behaviour related to pain. Also their behaviour, beliefs and perceptions can have a significant impact on the child's response to pain (*33*). The approaches used by parents and caregivers to console the child, such as rocking, touch and verbal reassurance must be considered when observing distressed behaviour.

Pain expression can differ markedly in **children with severe malnutrition** who are often under-stimulated and developmentally delayed due to malnutrition and/or concomitant chronic conditions. Such children often respond differently to pain compared to well-nourished children. Undernourished children may not express pain through facial expressions and crying, but may whimper or faintly moan instead and have limited physical responses because of underdevelopment and apathy (*16*).

2.3 Documentation of pain: the use of pain measurement tools

Several pain measurement tools have been developed to assess and document pain in children. There is need to recognize, evaluate, measure and monitor pain, and pain control strategies, using pain tools that are appropriate to the child's age, culture and condition. A number of tools have also been developed to address pain assessment in children unable to talk and in cognitively impaired children. Some degree of pain assessment is always possible, even in the critically-ill or cognitively-impaired child.

It is important to select psychometrically validated tools for the specific paediatric population and for persisting pain. No single pain intensity tool is appropriate across all ages or all types of pain. The majority of pain measurement tools have been developed and validated for acute pain. The evidence provided in this section primarily consists of systematic reviews by the Paediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) and by the Society of Pediatric Psychology Pain Assessment Task Force (SPP-ATF) (*32, 34–38*).

The most common pain measurement tools – **pain intensity scales** – rely on the capacity to quantify pain. They are often based on the concept of counting. Pain severity can be determined by teaching children to use quantitative pain scales. Practical tools based on the concept of quantifying and counting are appropriate for all cultures. The capacity of quantifying and counting depends on the age and developmental level of the child (*39, 40*). The following self-report pain scales (*Faces Pain Scale-Revised, Poker Chip Tool*, the *Visual Analogue Scale (VAS)*, and the *Oucher Photographic* and *Numerical Rating Scale (NRS)* have been recommended to measure pain intensity in children with acute and persisting pain by both the Ped-IMMPACT and SPP-ATF reviews. Table 2.1 provides comprehensive information about these tools including the applicable age range. These different tools are validated for measurement of pain intensity in children above three to four years old or above eight years old.

Table 2.1 List of self-report measuring tools for pain intensity

Tool and acronym (original citation)	Applicable age range and method	Comments (strengths, weaknesses and limitations, cultural validation)	Language	Ease of use	Availability, cost, source
Faces Pain Scale-Revised (FPS-R) (*41*)	4–12 years – self-report by child	Faces are line drawings with no ethnicity distinctions ranging from a neutral expression to one of intense pain but without tears. Simple, quick to use and requires minimal instructions.	Available in 47 languages	Easy to administer and score, readily reproducible by photocopying.	All translations available at no cost at: http://www.iasp-pain.org/fpsr/
Pieces of Hurt tool/ Poker Chip tool (*42*)	3–12 years – self-report by child	Based on concrete ordinal rating scale. Require confirmation that size-sorting task is developed in children. Weaknesses include cleaning the chips between patient use, the potential for losing chips and the limited number of response options (0–4). Only modest evidence of reliability and validity in preschool children between 3 and 4 years.	Arabic, English, Spanish, Thai	Simple, quick to use, require minimal instruction, easily reproducible, transported and disinfectable.	Instructions in English available at: http://painresearch.utah.edu/cancerpain/ch14.html

Tool and acronym (original citation)	Applicable age range and method	Comments (strengths, weaknesses and limitations, cultural validation)	Language	Ease of use	Availability, cost, source
Visual Analogue Scale (VAS) (*43*)	Above 8 years – self-report by child	Sensitive to change, correlates significantly with parents' and/or caretakers' ratings of children's pain. Retrospective self-report has more recall bias, requires a high degree of abstraction to indicate, on a line, the different verbal expressions for varying pain intensity and unpleasantness.	Chinese, English, French, Italian, the main Nigerian languages (Hausa, Igbo, Yoruba) (*44*), Portuguese, Spanish	Easy to administer and score, readily reproducible, but photocopying may alter the scale by increasing or decreasing the length of the line.	Available at no cost at: http://www.partnersagainstpain.com/printouts/A7012AS1.pdf
(a) The Oucher Photographic (b) 0–10 Numerical Rating Scale (*45*)	(a) 3–12 years (b) Above 8 years – self-report by child	(a) A colour photographic scale of a child's face with different pain expressions for younger children and a NRS of 0–10 for older children. There are four versions of the photographic scale: African-American, Asian, Caucasian and Hispanic child populations. (b) The NRS can be administered verbally by asking the child to verbally estimate his/her pain level on a 0–10 pain scale, with 0 representing no pain and 10 representing the worst pain.	English	Simple to use. (a) The Oucher photographic NRS requires costly colour printing. (b) The NRS can be administered verbally without any printed material.	Available at: (a) http://www.oucher.org/differences.html (b) http://painconsortium.nih.gov/pain_scales/NumericRatingScale.pdf

The tools that measure pain in children unable to talk and cognitively-impaired children do so by quantifying and rating behavioural signs. Currently, all the observational tools to measure behaviour have been developed for acute pain related to diagnostic procedures, such as bone marrow aspiration, lumbar puncture or post-operative pain.

No validated tool can support pain measurement in persisting pain settings (*32, 46–48*). There is also variability among the expressions of pain in preverbal children and cognitively impaired children. This can additionally be influenced by the disease and condition of the child, such as in malnourished children. The individual child should be observed to detect behaviour that expresses pain.

The child's initial pain and his or her response to interventions should be assessed on a regular basis and when there are changes in the child's clinical condition, new reports of pain, increased levels of pain or changes in the child's activity. Pain-control therapies should be adjusted accordingly. In children with stable persisting pain, pain should still be assessed on a regular basis with shorter intervals. Measurements should be recorded over time in the child's clinical chart or by the child or his/her caregivers in a journal.

In addition to pain severity measurements, it is important to record the location of pain, characteristics, onset and duration. There are conditions where the pain intensity changes not only over time, but also in location and characteristics. In these cases, tools measuring all these dimensions may be more appropriate than just pain intensity measurements, such as for vaso-occlusive crises in sickle cell disease (Box 2.2) (*49*).

Box 2.2 Multidimensional assessment of episodic pain in children with sickle cell disease

Pain control for children with SCD vaso-occlusive episodes requires frequent systematic pain assessments and continuous adjustments of pharmacological treatment. One of the more debilitating aspects of vaso-occlusive crises is the unpredictable nature in terms of frequency, intensity, affected sites and duration of pain. All these aspects of pain need to be assessed in children with SCD (*25*). Sickle cell disease pain is complex and a numerical rating of pain intensity cannot adequately assess its characteristics. The pain from SCD varies in intensity, location, quality and temporal patterns. The measurement of this kind of pain requires the use of multidimensional pain assessment tools (*50*). The Adolescent Pediatric Pain Tool is a multidimensional pain assessment instrument, which has demonstrated its validity and clinical utility for children and adolescents with SCD in clinics, day hospitals and inpatient settings (*51*).

2.4 Defining criteria and selecting a pain measurement tool in clinical settings

In a clinical setting, the selection of pain scales and pain measurement tools should be guided by the following criteria:

- appropriate for the age group, developmental level and sociocultural context, and covers all dimensions of persisting pain in children;
- easy to understand and to explain to a child, the parents/caregivers and health-care providers;
- process of scoring is easy, short and quick;
- the data obtained is recordable and easy to interpret;
- readily available and inexpensive;
- require minimal material or equipment in terms of paper, pencil, colours, etc.;
- if reusable, easy to disinfect;
- easy to carry;
- evidence-based (validity, reliability, responsiveness to change, interpretability and feasibility established by research);
- tested in many languages and cultures and widely used.

(Adapted from (*39*))

It is important to choose one tool and use it routinely so that the child, the parents and/or the caregivers, and the health-care provider, become familiar with its significance to the individual child. Health-care providers should be trained in administering and interpreting the tools. Box 2.3 provides general guidance on how and when to introduce a child to a self-report pain measurement tool and how to record and interpret the scores.

Box 2.3 Step-by-step guidance for administering and interpreting a self-report pain scale

- If possible, introduce the child to the pain scale when he or she is not in pain, because pain will impair the child's concentration.
- Explain to the child that the measure is for the pain severity and not for their anxiety or fear of pain.
- Offer the child a chance to practice with the scale by rating hypothetical situations that produce no, low and high levels of pain.
- When possible, obtain regular pain ratings and observe the effect of pain-relieving interventions as well as clinical interventions known to increase pain, such as injections.
- Take recorded pain scores into account when planning treatment.
- Use observational measures with very young children or the cognitively impaired.
- Avoid asking the child to score pain he/she experienced a long time ago as recalled pain scores are unlikely to be accurate.
- Obtaining pain scores should not be a substitute for talking to children and their narrative should always be obtained.
- Discrepancies arising in the pain scores provided by the child, parent and clinician can often be resolved through discussion.

Source: adapted from (*39*).

2.5 Assessment of other parameters in children with persisting pain

Children experiencing pain can be limited in their physical activities as well as in their development because they face difficulties in concentrating and learning. If their pain is not managed well, their quality of life can be affected, resulting in impaired physical functioning, anxiety, fear, stress and sleep disruption (*52, 53*). In addition to the measurement of pain intensity, duration, frequency and location, emotional function should also be assessed. Generic or disease-specific tools exist to measure these different functions in the child. However, such tools are not applicable to all clinical settings and are often used to assess the efficacy of interventions in clinical studies.

Children and adolescents with persisting pain can be impaired during normal activities, such as sitting or walking, or during more vigorous activities, such as running and sports. Persisting and recurrent pain significantly interfere with the social functioning of children and adolescents (*52, 54–56*). It is, therefore, important to assess the extent of the child's **restriction in physical and social activities**, including school-related activities, during the initial evaluation of pain and the implementation of the pain management plan.

Emotional disturbances, such as fear, anxiety and emotional stress, can be both a risk factor and an outcome of pain and functional disability. Some of the common signs of distress in children with pain are irritability, tantrums, restlessness, sleep problems, falling school performance, anxiety, a feeling of hopelessness, change in eating habits, anger, a preference to be alone, avoiding friends, etc. There are tools that assess depression and anxiety in children. These are important aspects that need to be included in a comprehensive pain assessment (*57, 58*).

Children with persisting pain often experience **sleeping difficulties**. Difficulties in falling asleep, frequent arousals, night and early morning awakening, and poor sleep quality are some of the common complaints (*59, 60*). Sleep disorders may increase pain experience or may be an outcome of persisting pain.

Children often cope with pain differently from adults. Also, older children may have better **coping skills** than younger children. Depending on age and temperament, some children may withdraw or become unduly quiet, while others act aggressively, throw tantrums expressing anger, impatience and anxiety. Ineffective, negative coping mechanisms may influence a child's physical, psychosocial and emotional health, and quality of life. Catastrophic thinking about pain or negative thinking (the fear of pain and its consequences) increases physical symptoms, pain severity, and contributes to functional disability and psychological distress (*61, 62*).

Children coping well with their pain take an active interest in their surroundings and daily life activities, look, touch, and ask questions. They display less distress than those who use avoidance behaviours (*63*). It is important to help identify and promote behaviours that reduce the negative impact of persisting pain (*64*).

2.6 Overcoming the challenges of assessing persisting pain in children

Negative attitudes and poor knowledge of pain and its assessment and measurement are barriers to pain management in children. This has been experienced in a number of settings and diseases (*65*). Inadequate training, language barriers, cultural diversity and limited resources may prevent health-care workers from providing basic pain care (*66*). Managing pain starts with recognizing and assessing pain. Therefore, planning pain assessment as an integral element of pain management at all levels of the health system is crucial to overcome barriers to assessing persisting pain in children.

Health-care providers may perceive the assessment of persisting pain as a time-consuming process. Therefore, in order to provide quality treatment **educating health-care providers** about the importance of pain assessment is necessary. Pain assessment is a mandatory part of pain management similar to the assessment of vital signs in managing disorders affecting other system functions. Health-care providers should be trained in the techniques for assessing and grading pain with easy-to-use tools, as well as in interviewing skills for children and parents/caregivers. They should also be able to consider other components such as coping mechanisms, anxiety and quality of life. Training of health professionals should also include interviewing skills in dealing with children and parents/caregivers, and knowledge of how to cross any cultural and language barriers to include parents and caregivers in the pain management plan of their child.

Health professionals and the child's family have **a joint responsibility** to achieve the best outcome Parents and caregivers can support pain assessment and the effectiveness of the pain management plan if adequately trained by health-care providers.

3 PHARMACOLOGICAL TREATMENT STRATEGIES

PATIENT-LEVEL GUIDELINES FOR HEALTH PROFESSIONALS

The pharmacological treatment strategies described in this chapter are based on the recommendations made by the WHO Guidelines Development Group. They provide health professionals and policy-makers with guidance on the pharmacological management of persisting pain in children with medical illnesses. These treatment guidelines should be part of a comprehensive approach also including non-pharmacological treatment. The considerations of the panel when formulating the clinical recommendations (quality of evidence, benefits/risks ratio, values, acceptability, feasibility, costs, policy and research agenda) are reported in Annex 2. ***Background to the clinical recommendations.*** The evidence used to formulate each recommendation according to the GRADE approach is reported in Annex 4. ***Evidence retrieval and appraisal***.

Principle

Optimal pain management may require a comprehensive approach comprising a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacological strategies. A comprehensive approach is possible even in resource-limited settings.

3.1 Principles for the pharmacological management of pain

Correct use of analgesic medicines will relieve pain in most children with persisting pain due to medical illness and relies on the following key concepts:

- using a two-step strategy
- dosing at regular intervals
- using the appropriate route of administration
- adapting treatment to the individual child

The latter three principles were introduced by WHO as "by the clock", "by the mouth" and "by the individual" in 1986, together with the introduction of the three step-ladder of pain relief. This three-step ladder has been abandoned now for children in favour of a two-step approach (*14*).

3.2 Treating pain using a two-step strategy

Recommendation

1. It is recommended to use the analgesic treatment in two steps according to the child's level of pain severity.
   Strong recommendation, very low quality of evidence

Although there are a limited number of analgesic medicines that can be safely used in children, it is still possible to provide adequate analgesia with a two-step approach. This two-step strategy consists of a choice of category of analgesic medicines according to the child's level of pain severity: for children assessed as having mild pain, paracetamol and ibuprofen should be considered as first options and in children assessed as being in moderate to severe pain, the administration of an opioid should be considered.

3.2.1 The first step: mild pain

Recommendations

2. Paracetamol and ibuprofen are the medicines of choice in the first step (mild pain).
3. Both paracetamol and ibuprofen need to be made available for treatment in the first step.
   Strong recommendations, low quality evidence

In children above three months of age who can take oral medication and whose pain is assessed as being mild, paracetamol and ibuprofen are the medicines of choice. For children below three months of age, the only option is paracetamol.

No other non-steroidal anti-inflammatory drug (NSAID) has been sufficiently studied in paediatrics for efficacy and safety to be recommended as an alternative to ibuprofen. Although there is evidence of the superior analgesic properties of ibuprofen versus paracetamol in acute pain, this is considered low-quality evidence because studies were performed in acute pain settings and because of the absence of long-term safety evidence for its continuous use in persisting pain. Both paracetamol and ibuprofen have potential toxicity: there are concerns about potential renal and gastrointestinal toxicity, and bleeding with ibuprofen and other NSAIDs; and there are risks of hepatotoxicity and acute overdose associated with paracetamol.

Both medicines should both be made available as the first step in the paediatric pain management strategy for mild pain. They are widely available in child-appropriate dosage forms, such as oral liquids, and are relatively inexpensive. However, development of appropriate oral solid dosage forms for both medicines should be a priority. An oral solid formulation will be better accepted by children, if it is divisible and dispersible, allows easier administration by health-care providers and caregivers, requires only a small quantity of water for administration, and ensures a more accurate dosage than traditional tablets.

3.2.2 The second step: moderate to severe pain

If pain severity associated with a medical illness is assessed as moderate or severe, the administration of a strong opioid is necessary. Morphine is the medicine of choice for the second step, although other strong opioids should be considered and made available to ensure an alternative to morphine in case of intolerable side-effects.

The decision to prescribe and administer opioid analgesics bypassing the first step should be based on a clinical judgement of the severity of a child's pain, on careful considerations of the disability caused by pain, on the cause of the pain, and expected prognosis and other aspects. Guidance on the use of morphine and other strong opioids is provided under sections 3.6–3.13 and Annex 1.

3.2.3 Consideration of the two-step approach

The two-step approach is a more effective strategy for the pharmacological management of persisting pain in children with medical illness than the three-step analgesic ladder, which was introduced by WHO in 1986. The three-step analgesic ladder recommended the use of codeine as a weak opioid for the treatment of moderate pain, while the two-step approach considers the use of low doses of strong opioid analgesics for the treatment of moderate pain.

The benefits of using an effective strong opioid analgesic outweigh the benefits of intermediate potency opioids in the paediatric population (see Box 3.1 regarding codeine) and although recognized, the risks associated with strong opioids are acceptable when compared with the uncertainty associated with the response to codeine and tramadol in children.

However, as new data emerges on the safety and efficacy of tramadol or other alternative intermediate potency analgesics for the management of persisting pain in children, the two-step strategy may be revised.

Box 3.1 Excluded medicine for pain relief

Codeine
Codeine is a "*weak*" opioid that is widely available and has been previously recommended to control moderate pain. However, it presents well-known safety and efficacy problems related to genetic variability in biotransformation. Codeine is a prodrug that is converted into its active metabolite morphine by the enzyme CYP2D6. The efficacy of a prodrug depends on the amount of active metabolite formed. Variable expressions of the enzymes involved in the biotransformation of prodrugs can lead to substantial inter-individual and inter-ethnic differences in the conversion rate and the plasma concentration of the active metabolite. In the fetus, CYP2D6 activity is absent or less than 1% of adult values. It increases after birth, but it is estimated to be no higher than 25% of the adult values in children below five years. As a consequence, the analgesic effect is (very) low or absent in neonates and young children.

Furthermore, the percentage of poor metabolizers can vary in ethnic groups from 1% to 30%, resulting in ineffectiveness in large numbers of patients, including children (*67, 68*). Conversely, individuals who metabolize codeine quickly and extensively are at risk of severe opioid toxicity, given the high and uncontrolled conversion of codeine into morphine (*69*).

Insufficient data on other intermediate potency opioids
Tramadol is another analgesic with opioid effects that has been considered for the control of moderate pain. However, there is currently no available evidence for its comparative effectiveness and safety in children. Furthermore, tramadol is not licensed for paediatric use in several countries. More research on tramadol and other intermediate potency opioids is needed.

3.3 Treating pain at regular intervals

Principle

When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals ("by the clock" and not on an "as needed" basis).

Medication should be administered on a regular schedule for persisting pain, rather than on an "as required basis", unless pain episodes are truly intermittent and unpredictable. Children should, therefore, receive analgesics at regular intervals, with the addition of "rescue doses" for intermittent and breakthrough pain. Guidance on treatment of breakthrough pain is provided in Section 3.11 *Treatment of breakthrough pain*.

3.4 Treating pain by the appropriate route

Medicines should be administered to children by the simplest, most effective, and least painful route, making oral formulations the most convenient and the least expensive route of administration. The choice of alternative routes of administration, such as intravenous (IV), subcutaneous (SC), rectal or transdermal when the oral route is not available should be based on clinical judgement, availability and patient preference. The intramuscular (IM) route of administration is painful and is to be avoided. The rectal route has an unreliable bioavailability, both for paracetamol and morphine, which limits its applicability (*70*). The feasibility of employing different routes of administration depends on the setting. Guidance on routes of administration for opioid analgesics for step two is reported in Section 3.10 *Routes of administration*.

3.5 Tailoring pain treatment to the individual child

Principle

The treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis.

Opioid analgesics should be titrated on an individual basis, so the dose should be adapted in steps until the correct dosage has been found, based on the patient's reaction to the medicine. There is no specific or maximum dose of opioids that can be predicted in any individual case. The correct dose should be determined in collaboration with the patient to achieve the best possible pain relief with side-effects acceptable to the patient.

3.5.1 Non-opioid analgesics

The use of paracetamol and ibuprofen (and other NSAIDs) should be restricted to the recommended dosing regimen based on the age and weight of the child to avoid serious toxicity (Table 3.1 and Annex 1. *Pharmacological profiles*).

Consideration should also be given to certain conditions that influence the capacity of the child to metabolize paracetamol and ibuprofen, such as malnutrition, poor nutritional state and administration of other medicines.

Table 3.1 Non-opioid analgesics for the relief of pain in neonates, infants and children

Medicine	Dose (oral route)			Maximum daily dose
	Neonates from 0 to 29 days	Infants from 30 days to 3 months	Infants from 3 to 12 months or child from 1 to 12 years	
Paracetamol	5–10 mg/kg every 6–8 hrs[a]	10 mg/kg every 4–6 hrs[a]	10–15 mg/kg every 4–6 hrs[a,b]	Neonates, infants and children: 4 doses/day
Ibuprofen			5–10 mg/kg every 6–8 hrs	Child: 40 mg/kg/day

[a] Children who are malnourished or in a poor nutritional state are more likely to be susceptible to toxicity at standard dose regimens due to reduced natural detoxifying glutathione enzyme.

[b] Maximum of 1 gram at a time.

3.5.2 Opioid analgesics

To obtain a dose that provides adequate relief of pain with an acceptable degree of side-effects the doses of morphine or other strong opioids need to be gradually increased until effective. Unlike paracetamol and NSAIDs, there is no upper dosage limit for opioid analgesics because there is no "ceiling" analgesic effect. The appropriate dose is the dose that produces pain relief for the individual child. The goal of titration to pain relief is to select a dose that prevents the child from experiencing pain between two doses using the lowest effective dose. This is best achieved by frequent assessment of the child's pain relief response and adjusting the analgesic doses as necessary.

The opioid dose that effectively relieves pain varies widely between children, and in the same child at different times, and should, therefore, be based on the child's pain severity assessment. Large opioid doses given at frequent intervals may be necessary to control pain in some children; these doses may be regarded as appropriate, provided that the side-effects are minimal or can be managed with other medicines. An alternative opioid should be tried if patients experience unacceptable side-effects such as nausea, vomiting, sedation and confusion.

Starting doses are illustrated in tables 3.2–3.4 (below). This information is extracted from Annex 1, *Pharmacological profiles*, where more detailed information is provided. After a starting dose according to dosage tables 3.2–3.4, the dosage should be adjusted on an individual basis to the level that it is effective (with no maximum dose, unless further increase is not possible because of untreatable side-effects). The maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% while monitoring the patient carefully.
Please note that 1 milligram (mg) = 1000 microgram (mcg).

Long-term opioid use is usually associated with constipation and patients should also receive a combination of a stimulant laxative and a stool softener prophylactically.

3.6 Strong opioids essential in pain treatment

Recommendation

4. The use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses.
   Strong recommendation, low quality of evidence

There is no other class of medicines than strong opioids that is effective in the treatment of moderate and severe pain. Therefore, strong opioids are an essential element in pain management.

Unfortunately, fear and lack of knowledge about the use of opioids in children as well as in adults are often a barrier to the relief of pain. The efficacy of strong opioids in the relief of pain is established; indirect evidence from adult chronic non-cancer pain (*71*) as well as the considerations (*72*) which supported the inclusion of morphine in the *WHO model list of essential medicines for children* (EMLc) (*73*) substantiate its use in children to relieve moderate to severe pain. The risks associated with severe side-effects and mortality arising from medication errors are real, but substantially preventable through good pain management education and appropriate risk management systems.

Countries should review, and if neccessary, revise their policies and regulations to ensure availability and accessibility of opioid analgesics for the relief of moderate to severe pain in children in order to enable health-care professionals to provide adequate pain relief in accordance with these guidelines.

Chapter 4. *Improving access to pain relief in health systems*, Annex 3. *Background to the health system recommendations* and Annex 6. *Opioid analgesics and international conventions* look at the issues related to policies, regulations and health systems, which determine access to pain relief.

3.7 Choice of strong opioids

Recommendations

5. Morphine is recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses.
6. There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.
7. Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability including patient-related factors.
   Strong recommendations, low quality of evidence

Morphine is well established as the first-line strong opioid: it is relatively inexpensive and a wide range of morphine formulations are included in the EMLc as reported in Box 3.2. The available evidence on comparisons between different opioids and routes of administration in children relate to acute and post-operative pain. There is a need for comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use in children with persisting pain due to medical illnesses. Child appropriate dosage formulations for opioids are currently limited to oral liquids, which are often prepared as required by pharmacists. The strengths of opioids currently available on the market make it difficult to administer the intravenous doses required for young infants and neonates. The development of safer dosage formulations for these very young age groups should become a high priority.

Pethidine (also called: mepiridine) should no longer be used, because it is considered inferior to morphine due to its toxicity on the central nervous system (*74*).

Box 3.2 Formulations of morphine listed in the *WHO model list of essential medicines for children*, 2010

- *Injection:* 10 mg in 1 ml ampoule (morphine hydrochloride or morphine sulfate).
- *Granules (prolonged-release) (to mix with water):* 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).
- *Oral liquid:* 10 mg/5 ml (morphine hydrochloride or morphine sulfate).
- *Tablet (immediate-release):* 10 mg (morphine sulfate).
- *Tablet (prolonged-release):* 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).

Source: (*73*)

3.8 Immediate-release and prolonged-release oral morphine

Recommendations

8. It is strongly recommended that immediate-release oral morphine formulations be available for the treatment of persistent pain in children with medical illnesses.
9. It is also recommended that child-appropriate prolonged-release oral dosage forms be available, if affordable.
   Strong recommendations, low quality of evidence

Oral tablet morphine formulations are commercially available both as immediate-release and prolonged-release. Immediate-release tablets are used for titrating morphine dosage for the individual child and defining the adequate dose for pain control. They are also indispensable for the management of episodic or breakthrough pain.

Prolonged-release oral formulations allow for longer dose intervals, therefore, improving the patient's compliance by reducing dose frequency. Prolonged-release oral formulations of morphine are administered every 8 to 12 hours (compared with every 4 hours for immediate-release tablets) but are unsuitable for the treatment of breakthrough pain. Therefore, availability of immediate-release formulations has priority over prolonged-release formulations of morphine.

Oral morphine solution is used when a child is not able to swallow tablets. Prolonged-release tablets cannot be crushed, chewed or cut, but prolonged-release granules can replace prolonged-release tablets in such a case.

Although relatively inexpensive, in some countries, immediate-release morphine tablets are neither marketed in the private sector nor in the public sector. Efforts to ensure availability should be a priority. If affordable, prolonged-released morphine should also be made available to improve patient compliance and facilitate administration at regular intervals ("by the clock"). Key formulations for management of pain in children should be included in the national essential medicines lists and in the national medicines policies and implementation plans (Box 3.3).

Box 3.3 Guidance for selection and procurement of morphine oral formulations

When selecting morphine formulations for the management of moderate to severe pain in children, priority should be given to the selection and procurement of immediate-release formulations (tablets and liquids).

Liquid preparations allow for easier dose administration than tablets in infants and small children, although they may be more expensive and present challenges related to stability, portability and storage.

Morphine powder for preparing oral liquid preparations extemporaneously can often overcome affordability and availability barriers to suitable paediatric liquid formulations. Their preparation requires access to pharmacists and suitable ingredients for physical, chemical and microbiological stability, as well as standards to ensure quality. Compounding of morphine powder may be subject to legal restrictions and regulations related to where the compounding is carried out, such as in hospitals or community pharmacies. Extemporaneous preparations should be compounded in pharmacy settings and are intended for short-term use. This has to be considered when planning their use within the health-care service.

Prolonged-release morphine tablets should be made available after securing immediate-release formulations. Prolonged-release morphine formulations do not allow for opioid titration and they are, therefore, not suitable as stand-alone formulations for children.

Prolonged-release tablets cannot be chewed, crushed or cut. Therefore, when procuring such formulations for use in children, reference should be made to the strength of prolonged-released formulations listed in the *WHO model list of essential medicines for children*, 2010 (Box 3.2).

3.9 Opioid switching

The terms "opioid switching" and "opioid rotation" are often used with different or interchangeable meanings in clinical settings and in the scientific literature. For the purposes of these guidelines, opioid switching is defined as: *the clinical practice of changing to an alternative opioid because of an inadequate analgesic effect and/or dose-limiting side-effects.* For the purposes of these guidelines, opioid rotation is defined as: *the practice of changing between different opioids in a set schedule to prevent potential adverse effects and limit dose escalation*. However, currently there is no evidence in children or in adults to recommend opioid rotation to prevent side-effects or dose escalation.

Recommendations

10. Switching opioids and/or route of administration in children is strongly recommended in the presence of inadequate analgesic effect with intolerable side-effects.
11. Alternative opioids and/or dosage forms as an alternative to oral morphine should be available to practitioners, in addition to morphine, if possible.
12. Routine rotation of opioids is not recommended.
    Strong recommendations, low quality of evidence

Optimal titration of an opioid in an individual child is crucial before considering switching to another opioid. **Irrational switching should be avoided**; switching should only be considered when the administered medicine has been adequately titrated but the analgesic response is inadequate and side-effects experienced by the child are intolerable.

Safety while switching opioids should always be ensured, in particular due regard to the risk of opioid overdose. For the purpose of these guidelines, fentanyl, hydromorphone, methadone and oxycodone formulations have been considered alternatives to morphine for switching in children with persisting pain. Risks associated with switching from one opioid to another are considered to be manageable if age-appropriate dose conversion tables for different opioids are available and clinical practitioners are adequately trained in this practice. Other factors to consider in the titration and conversion from one opioid to another are: the bioavailability of the formulation; interactions with other medicines; renal and hepatic clearance; and the opioid analgesics that have previously been used to relieve the child's pain.

For approximate conversion rates for switching between parenteral and oral administration see Table 3.5 (below).

3.10 Routes of administration

Recommendations

13. Oral administration of opioids is the recommended route of administration.
14. The choice of alternative routes of administration when the oral route is not available should be based on clinical judgement, availability, feasibility and patient preference.
15. The intramuscular route of administration is to be avoided in children.
    Strong recommendations, very low quality of evidence

There is inadequate evidence to support a preference for alternative routes of administration other than the oral route. The available studies dealt with the management of acute or post-operative pain and did not provide conclusive evidence to guide recommendations. Trials are needed for future guidance on the use of alternative routes. The subcutaneous route (via continuous infusion or intermittent bolus through an indwelling catheter) is widely used and could be a valuable alternative.

Intramuscular injections are to be avoided as they cause additional pain and are, therefore, not an acceptable route of administration given that other alternatives exist. Furthermore, children frightened by IM administration may not request pain relief or may deny being in pain.

As reported above, the potency of the opioids needs to be considered when choosing a route of administration. For example, there could be considerable risks associated with the intranasal administration for a rapid onset of high potency opioids in the management of breakthrough pain.

The feasibility of employing different routes of administration depends on the setting, with due consideration of the cost, staff time and training involved to safely administer analgesia using other routes than the oral route.

Patient-controlled analgesia (PCA) is an approach to intravenous or subcutaneous administration of medicines. It allows children from approximately the age of seven to self-administer "rescue" doses of analgesics for breakthrough pain. A pre-set dose is delivered into an infusion line by a computer-driven pump. For safety, there is a limited lock-out period after each dose so that additional doses cannot be delivered before a specified time has elapsed. Patient-controlled analgesia may be used alone or with concurrent continuous infusions. It should be noted that PCA techniques might require access to expensive equipment.

3.11 Treatment of breakthrough pain

Recommendations

16. A careful distinction between end-of-dose pain episodes, incident pain related to movement or procedure, and breakthrough pain is needed.

17. It is strongly recommended that children with persisting pain receive regular medication to control pain and also appropriate medicines for breakthrough pain.
    Strong recommendations, very low quality of evidence

There is insufficient evidence to recommend a particular opioid or route of administration for breakthrough pain in children. There is a need to make an appropriate choice of treatment modality based on clinical judgement, availability, pharmacological considerations and patient-related factors.

Breakthrough pain is pain that is of sudden onset, occurs for short periods of time and it is usually severe. This type of pain is common in patients with cancer who often have a background level of pain controlled by medicines, but periodically, the pain "breaks through" the medication. It should not be confused with incident pain due to procedures and movements or with end-of-dose pain.

Currently, immediate-release formulations of morphine and IV morphine are the most commonly used formulations for breakthrough pain in children. Rescue doses of opioid may be calculated as 5–10% of the total daily opioid requirement. If repeated breakthrough doses are required, the regular baseline morphine dose should be adjusted.

Alternative formulations of opioids given by alternative routes of administration have been investigated for breakthrough pain in adults, but at present there are no data to support their use in children. Research into the optimal choice of opioid and route of administration for rapidly effective relief of breakthrough pain in children with persisting pain is needed to inform future clinical practice.

3.12 Tolerance, withdrawal and dependence syndrome

Tolerance to opioids occurs when the body becomes accustomed to a certain dose of the medicine and therefore an increased dose is required to obtain the same effect. This physiological phenomenon is not to be confused with **dependence syndrome**, which involves behavioural and cognitive phenomena, including a strong desire to take the psychoactive drug, persisting in its use despite harmful consequences, and giving a higher priority to drug use than to other activities and obligations (*75*).

If opioid analgesics are suddenly withdrawn, children display neurological signs, such as irritability, anxiety, insomnia, agitation, increased muscle tone, and abnormal tremors, and experience gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, diarrhoea and poor appetite. **Withdrawal syndrome** in children may also include tachypnea, tachycardia, fever, sweating and hypertension. Several scoring systems exist measuring withdrawal, such as the Neonatal Abstinence Score, which was originally developed to rank symptoms in neonates exposed to intrauterine opioids, but has been subsequently adapted for use in older children (*76–78*).

The risk of opioid withdrawal increases with the duration and dosages of the opioid. Children who have received significant doses of opioid analgesics for a long time will experience opioid withdrawal syndrome if it is suddenly discontinued. Opioid weaning can be done safely without posing significant health risk to the patient. From the medical standpoint, weaning opioids should be done slowly by tapering the opioid dose. For short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval. In the case of a long-term therapy protocol, the dose should be reduced not more than 10-20% per week (*79, 80*). These pharmacological approaches should be accompanied by measurement of withdrawal symptoms using a scoring system.

3.13 Opioid overdose

Opioid overdose can be caused by miscalculation of the initial dose required for a child. It can also occur when doses are not correctly calculated during opioid switching or when prolonged-release formulations are erroneously used instead of short-acting ones. It is very important that health-care providers are trained to prescribe and administer the opioid analgesic formulations available for pain relief in their health service in order to avoid errors in the handling of these medicines. Any new opioid analgesic and any new formulation should only be introduced into a health service with appropriate training of health-care providers on rational medical use.

When opioid overdose occurs, the child may have respiratory depression – usually accompanied by the classical sign of pinpoint pupils – which can lead to coma. Naloxone is a specific antidote, but care in its administration is needed in order not to precipitate opioid withdrawal syndrome. Moderate opioid overdose can be managed with assisted ventilation, while naloxone doses starting at 1 microgram (mcg)/kg are titrated over time, e.g. every 3 minutes, until the necessary dose is found. A low-dose infusion under close monitoring may be required thereafter to maintain wakefulness until the adverse effect of the opioid overdose resolves (*81*).

In children receiving regular opioid treatment for pain and children who are opioid-tolerant, naloxone needs to be used with caution, in order not to evoke extreme pain or withdrawal reactions. Doses needed to revert opioid overdose in such patients are lower than those normally indicated for opioid intoxication and overdose in opioid-naive children (Annex 1. *Pharmacological profiles*).

Table 3.2 Starting dosages for opioid analgesics for opioid-naive neonates

Medicine	Route of administration	Starting dose
Morphine	IV injection[a]	25–50 mcg/kg every 6 hrs
	SC injection	
	IV infusion	Initial IV dose[a] 25–50 mcg/kg, then 5–10 mcg/kg/hr 100 mcg/kg every 6 or 4 hrs
Fentanyl	IV injection[b]	1–2 mcg/kg every 2–4 hrs[c]
	IV infusion[b]	Initial IV dose[c] 1–2 mcg/kg, then 0.5–1 mcg/kg/hr

[a] Administer IV morphine slowly over at least 5 minutes.

[b] The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.

[c] Administer IV fentanyl slowly over 3–5 minutes.

Table 3.3 Starting dosages for opioid analgesics in opioid-naive infants (1 month – 1 year)

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	80–200 mcg/kg every 4 hrs
	IV injection[a]	*1–6 months*: 100 mcg/kg every 6 hrs *6–12 months*: 100 mcg/kg every 4 hrs (max 2.5 mg /dose)
	SC injection	
	IV infusion[a]	*1–6 months*: Initial IV dose: 50 mcg/kg, then: 10–30 mcg/kg/hr *6–12 months*: Initial IV dose: 100–200 mcg/kg, then: 20–30 mcg/kg/hr
	SC infusion	1–3 months: 10 mcg/kg/hr 3–12 months: 20 mcg/kg/hr
Fentanyl[b]	IV injection	1–2 mcg/kg every 2–4 hrs[c]
	IV infusion	Initial IV dose 1–2 mcg/kg[c], then 0.5–1 mcg/kg/hr
Oxycodone	Oral (immediate release)	50–125 mcg/kg every 4 hours

[a] Administer IV morphine slowly over at least 5 minutes.

[b] The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.

[c] Administer IV fentanyl slowly over 3–5 minutes.

Table 3.4 Starting dosages for opioid analgesics in opioid-naive children (1–12 years)

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	1–2 years: 200–400 mcg/kg every 4 hrs 2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg)
	Oral (prolonged release)	200–800 mcg/kg every 12 hrs
	IV injection[a]	1–2 years: 100 mcg/kg every 4 hrs 2–12 years: 100–200 mcg/kg every 4 hrs (max 2.5 mg)
	SC injection	
	IV Infusion	Initial IV dose : 100–200mcg/kg[a], then 20–30 mcg/kg/hr
	SC infusion	20 mcg/kg/hr
Fentanyl	IV injection	1–2 mcg/kg[b], repeated every 30–60 minutes
	IV infusion	Initial IV dose 1–2 mcg/kg[b], then 1 mcg/kg/hr
Hydromorphone[c]	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)
	IV injection[d] or SC injection	15 mcg/kg every 3–6 hrs
Methadone[e]	Oral (immediate release)	100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially)[f]
	IV injection[g] and SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hours (max 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hours

[a] Administer IV morphine slowly over at least 5 minutes.

[b] Administer IV fentanyl slowly over 3–5 minutes.

[c] Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.

[d] Administer IV hydromorphone slowly over 2–3 minutes.

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

[f] Methadone should initially be titrated like other strong opioids. The dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation. From then on dosage increases should be performed at intervals of one week or over and with a maximum increase of 50%.

[g] Administer IV methadone slowly over 3–5 minutes.

Table 3.5 Approximate dose ratios for switching between parenteral and oral dosage forms

Medicine	Dose ratio (parenteral : oral)
Morphine	1:2 – 1:3
Hydromorphone	1:2 – 1:5[a]
Methadone	1:1 – 1:2

[a] Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another. In converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose.

3.14 Adjuvant medicines

Adjuvant medicines have a primary indication other than for pain management, but have analgesic properties in some painful conditions. They may be co-administered with analgesics to enhance pain relief. Different categories of medicines have been investigated to determine their potential as adjuvants in relieving persisting pain and in specific cases, such as neuropathic pain, bone pain and pain associated with muscle spasm.

3.14.1 Steroids

Recommendation

18. The use of corticosteroids as adjuvant medicines is **not** recommended in the treatment of persisting pain in children with medical illnesses.
    Weak recommendation, very low quality of evidence

There are no studies in children to support adjuvant use of corticosteroids for pain relief and corticosteroids are identified with well-known adverse effects, particularly with chronic use. Corticosteroids are indicated in the management of specific other conditions, such as for the reduction of peritumour oedema, for raised intracranial pressure in CNS tumours, and for the treatment of neuropathic pain due to spinal cord or peripheral nerve compression.

3.14.2 Bone pain

BISPHOSPHONATES

Recommendation

19. The use of bisphosphonates as adjuvant medicines is **not** recommended in the treatment of bone pain in children.
    Weak recommendation, very low quality of evidence

There are no systematic reviews, randomized control trials or other studies on the use of bisphosphonates in the treatment of bone pain in children. In adults, one systematic review suggests that that bisphosphonates provide modest pain relief for patients with painful bony metastases (*82*). However, the use of bisphosphonates in adults is associated with potentially devastating adverse effects,

such as osteonecrosis of the jaw. Additional data on the safety and efficacy of bisphosphonates in children is needed to evaluate the potential of these medicines for bone pain.

3.14.3 Neuropathic pain

Data on the assessment and incidence of neuropathic pain in children are limited. Many of the neuropathic conditions seen in adults, such as diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, are rare in children. Children are affected by other neuropathic pain syndromes, including complex pain regional syndrome, phantom limb pain, spinal cord injury, trauma and post-operative neuropathic pain, and degenerative neuropathies (e.g. Guillain-Barré syndrome) (*9*).

ANTIDEPRESSANTS

At present, it is not possible to make a recommendation for or against the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) as adjuvant medicines in the treatment of neuropathic pain in children.

Tricyclic antidepressants. Clinical experience and trial data in adults support the use of tricyclic antidepresssants, such as amitriptyline or nortriptyline, in the treatment of neuropathic pain, such as post-herpetic neuralgia and diabetic neuropathy (*83*). However, although there is no evidence for the use of antidepressants for the management of pain in children, there is large clinical experience with the use of amitriptyline for pain management in children. Amitriptyline is widely available and inexpensive, and it is also included in the EMLc for depressive disorders. The general risks associated with overdoses of tricyclic antidepresssants are well described. In adults, adverse effects with tricyclic antidepresssants can be significant and can result in discontinuation of neuropathic pain treatment.

Selective serotonin reuptake inhibitors. There is limited evidence to suggest that the newer SSRIs may be effective for neuropathic pain treatment in adults (*83*) and there is no evidence for its use in relieving pain in children. The use of SSRIs in children and adolescents with depression has been associated with an increased risk of suicidal ideation and behaviour, although this risk has not been evaluated in adequately designed studies (*84*). Fluoxetine is listed in the EMLc for antidepressant disorders in children aged over eight years (*85*).

Trials in children concerning the safety and the efficacy of TCAs, SSRIs and newer antidepressants of the class of serotonin and norepinephrine reuptake inhibitors (SNRIs) for neuropathic pain are needed.

ANTICONVULSANTS

At present, it is not possible to make a recommendation for any anticonvulsant as an adjuvant in the management of neuropathic pain in children.

There is no evidence for the use of anticonvulsants for the management of neuropathic pain in children. No systematic reviews and/or randomized control trials in children were identified.

Carbamazepine. The use of carbamazepine to treat neuropathic pain in adults is common (*86*) and there is extensive experience with the use of carbamazepine in children in seizure management. Carbamazepine is listed in the EMLc as an anticonvulsant and is widely used.

Gabapentin. Gabapentin is registered for use as an anticonvulsant in children above the age of three years, but it has been promoted for use in neuropathic pain. However, there are no comparative studies with carbamazepine and no studies to determine its potential as an adjuvant in the treatment of persisting pain in children. Moreover, not all adult trial data have been published in their entirety and the evaluation of gabapentin's efficacy in reducing neuropathic pain in adults is yet to be systematically reviewed (*87*).

Trials are needed on both the safety and efficacy of carbamazepine and gabapentin in children as possible adjuvant medication for neuropathic pain.

KETAMINE

At present, it is not possible to make a recommendation regarding the benefits and risks of ketamine as an adjuvant to opioids for neuropathic pain in children.

There is limited evidence for ketamine in sub-anaesthetic (low) doses as an adjuvant to strong opioids in cancer pain in adults, which is insufficient to allow for any recommendation in clinical practice (*88*). There are no studies in children on the use of ketamine as an adjuvant to opioids for persisting pain. There is a need to perform trials on efficacy and safety of sub-anaesthetic (low) dose ketamine to investigate its potential as an adjuvant to opioids in refractory pain in children (i.e. pain that does not react sufficiently to some or all forms of treatment) and its side-effects. Ketamine is listed as anaesthetic agent in the EMLc.

LOCAL ANAESTHETICS

At present, it is not possible to make a recommendation regarding the benefits and risks of the systemic use of local anaesthetics for persisting neuropathic pain in children.

In adults, there is some evidence that intravenous lidocaine and its oral analogue mexiletine are more effective than placebo in decreasing neuropathic pain (*89*). No studies were retrieved in children and so further studies are needed to investigate the safety and efficacy of the systemic use of local anaesthetics in children with neuropathic pain from specific etiologies.

3.14.4 Pain associated with muscle spasm and spasticity

At present, it is not possible to make a recommendation for the use of benzodiazepines and/or baclofen as an adjuvant in the management of pain in children with muscle spasm and spasticity.

Both baclofen and benzodiazepines have long been used in the management of muscle spasm and spasticity, despite having no evidence base (*90, 91*). Similarly, there is no good evidence for the use of baclofen and benzodiazepines for pain associated with muscle spasm (*72*).

3.15 Research agenda

More data are necessary on long-term use of opioids in children, as well as studies comparing opioids in these age groups. Given the generalized lack of studies in neonates, infants and children, a research agenda has been defined to guide the scientific community's efforts to study a number of priority aspects in the pharmacological management of pain. It is possible to perform studies in the paediatric population provided that acceptable and appropriate trial methodology is used. The priorities identified by the Guidelines Development Group for a research agenda on pharmacological interventions for the treatment of pain in children are presented in Annex 5. *Research agenda*.

4 IMPROVING ACCESS TO PAIN RELIEF IN HEALTH SYSTEMS

4.1 The right to health, the right to be spared avoidable pain

The WHO Constitution defines health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*". The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being, without distinction of race, religion, political belief, or economic or social status. The Constitution also states that the health of all peoples is fundamental to the attainment of peace and security, and is dependent upon the fullest cooperation of individuals and states.

The United Nations Convention on the Rights of the Child (1989) reinforces "*the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health*". Signatory countries to the Convention "*shall strive to ensure that no child is deprived of his or her right of access to such health care services*" (*92*).

The United Nations Committee on Economic, Social and Cultural Rights recognized as part of this right to health "*attention and care for chronically and terminally ill persons, sparing them avoidable pain and enabling them to die with dignity*" (*93*). The United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, which sets the international control measures for most opioid analgesics, states that opioids are "*indispensable for the relief of pain and suffering and adequate provision must be made to ensure the availability of narcotic drugs for such purposes*" (*94*).

The countries signing these international conventions have mandated their governments to respect and act according to these rights. Government policies for the relief of pain should draw on these obligations.

4.2 International regulations on opioid analgesics

Countries operate within an international regulatory framework, which means that essential medicines for opioid analgesia, such as morphine, are subject to international control under the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol. The Convention outlines specific control requirements for narcotic substances and stresses the need to make opioid analgesics available for medical use, as reported above. This concept was reinforced in the United Nations Economic and Social Council's resolution 2005/25, which acknowledges the lack of access to opioids for pain relief for 80% of the world's population, and calls on Member States to remove barriers to the medical use of such analgesics while preventing their diversion for illicit use. This necessity was concurrently affirmed in the 2005 World Health Assembly resolution WHA 58.22 on cancer prevention and control.

Each signatory country to the international drug conventions should abide by the treaties by both ensuring the medical use of controlled substances and preventing their misuse. Countries should have implemented their obligations under the conventions in their national laws and regulations. However, some countries' laws and regulations may include provisions that go beyond the control requirements of the Single Convention on Narcotic Drugs, often hindering access to opioid analgesics. Assessing existing national drug control laws and regulations is a necessary step in improving access to opioid analgesia for moderate to severe pain. Authorities and policy-makers responsible for expanding pain relief treatment in the health system should start by assessing national control regulations for the production, procurement, storage, distribution, prescription, dispensing and administration of opioid analgesics. If a country does not have regulations that allow for the provision of opioids for medical purposes, these should be developed in accordance with the Single Convention on Narcotic Drugs. Those countries that have very strict laws should endeavour to make them less restrictive and more practicable. The World Health Organization has developed guidelines to ensure that a balance is achieved in national opioid control policy, last revised in 2011 (*95*).

Annex 6. *Opioid analgesics and international conventions* provides guidance on the main aspects to be considered under the international regulatory framework to make opioid analgesics available for pain relief. Operational and policy officers involved in improving access to pain management and opioid analgesics should be familiar with both the international and national regulations on opioid medicines.

4.3 Dimensions of a national pain treatment policy

The provision of pain management medicines needs to be supported by national policies and regulations. There are several dimensions and players in national policy that are necessary to achieve this goal. Apart from the control aspects of opioid analgesics, countries should consider the policy priorities for pain management. A national policy aiming at ensuring pain treatment within its health system should address several aspects impeding pain relief including attitudinal and educational barriers, and regulatory and supply barriers. Changing the regulatory framework for opioid analgesics, for example, by reducing the burden of dispensing procedures will not automatically result in increased access to pain medication as it will have no effect on unreasonable fear of opioid use ("opiophobia") among clinicians, pharmacists, nurses, patients and their families. In order to change attitudes, a major effort should be made to educate them on the rational use of opioid medicines. Similarly, overcoming supply barriers and making these medicines affordable within the health system will have little impact on their use if knowledge or regulatory barriers are not addressed.

A policy for improving pain management should be comprehensive in considering how the regulatory, educational and supply aspects will impact on pain management. This implies that governments should consider financial and health workforce resources when formulating policies and implementing pain management plans. Adequate management of pain is also feasible in countries with limited resources.

Pain clinicians, patients and caregivers associations can play an important role in engaging and supporting policy-makers to improve access to pain relief as an integrated component of the national health system. Analysis and research on the different types of barriers to adequate pain management and opioid availability is possible by involving all those associated in the provision of such treatment (from drug control agencies, to ministries of health departments, to health professional associations, to enforcement agencies, etc.).

4.4 Financing pain relief within the national system

As far as possible, governments should ensure that the most cost-effective and appropriate treatment is widely available and accessible. Pain treatment requires a multidisciplinary approach that combines pharmacological and non-pharmacological interventions. Both types of intervention entail costs. These guidelines were developed with the aim of retrieving and assessing the evidence and formulating recommendations on the pharmacological treatment of pain. They provide information on the essential elements to ensure the management of moderate to severe persisting pain in children with medical illnesses. Similarly, the choice of a non-pharmacological intervention needs to be guided by evidence supporting its use and by consideration of its cost-effectiveness and feasibility in relation to other interventions and to national financial and human resources.

The capacity of a country to provide pain relief as a part of the right to health relies on how its health financing system is designed. Patients' out-of-pocket spending will hardly allow them to access pain relief medicines, as well as other essential medicines. Studies have shown that prices of opioid analgesics in an out-of-pocket spending system are higher in developing countries than in developed

countries, making these essential medicines even more inaccessible to patients in need (*96, 97*). Out-of-pocket payments for health care foster inequalities among the population in accessing care and essential medicines and are barriers for the poorest (*98–100*). Reimbursing and increasing access to pain relief treatment within the context of either health insurance schemes, such as tax-funded health schemes, or social health insurance schemes can be a sustainable way of ensuring that pain relief is part of the right to health. Alternative financing mechanisms, such as community health insurance schemes, may be a suitable substitute in settings where the institutional framework for traditional health insurance schemes is weak.

The development and maintenance of pain treatment services take place within the broader context of national health-care financing. An understanding of the way health funds are underwritten and allocated is, therefore, important in planning the introduction and maintenance of pain treatment services. The use of risk-pooling schemes is a viable approach to paying for health services, as well as a more suitable way of developing and sustaining pain relief services at primary, secondary and tertiary health-care levels, and in the community.

4.5 Estimating needs for pain relief

Determining the total resources and associated costs needed to initiate and maintain pain relief services at all levels of the health system is a key element of strategic planning. A needs assessment is a formal systematic attempt to determine important gaps between what services are needed and those that are currently provided. The assessment involves documenting important gaps between current and desired outcomes, and then deciding in which order those gaps should be closed. Cost estimates should include different scenarios for scaling up services for both pharmacological and non-pharmacological interventions.

Needs assessments and cost estimates to improve pharmacological treatment of pain should comprise the following areas:

Educational needs

- *Training costs for health professionals in pain management*. Training gaps must be assessed and training plans on pharmacological interventions adopted at country level. This may include training of nurses and pharmacists, upgrading medical school curricula, and on-the-job training for health professionals. Once the national treatment guidelines for pain management have been prepared, they should be disseminated and countrywide training plans prepared.
- *Training costs for all officers and professionals involved in the procurement, supply and dispensing of opioid medicines*. Different types of training should be costed according to the targeted professionals and their needs for training on national drug control requirements and regulation of opioid analgesics. This should include health professionals, drug control regulators and enforcement officers. This type of training is needed when changes are made to national control policies, to ensure that the regulations are properly understood and applied. It may also be needed when inaccurate knowledge about national drug control regulations results in a problem of availability of these substances for medical use.
- *Advocacy costs for promoting and disseminating information on the medical use of opioid medicines for pain relief and palliative care to the general public*. Supplementary costs may need to be factored into the cost of training health-care providers and all officers and professionals playing a role in the procurement, supply, prescription and dispensing of medicines. In certain countries, the education of the general public on the medical use of opioid analgesics for pain relief may be crucial in overcoming misconceptions and biases towards these medicines.

Supply chain requirements and quantification of needs

- *Equipment costs to ensure no diversion of controlled opioid medicines*. Measures to avoid trade diversion during storage and distribution are generally in place in the private and public sectors. Drug control regulations require measures to safeguard opioid medicines (such as locked cupboards) in order to avoid the diversion of controlled medicines for illicit use. While these safeguards, which are defined at country level and not set by international drug conventions, should ensure that no diversion takes place, they should not impair the availability of drugs for medical use, both in terms of feasibility and costs.
- *Medicine costs, storage and distribution costs*. These should be factored into the budgets of national health systems for the supply of medicines. Parallel supply systems are usually not cost-effective (*101, 102*).
- *Quantification of needs*. The quantification of treatment needs is important in planning treatment services and in reviewing the accessibility of services to different population groups. It is the basis for forecasting the amount of medicines, in particular of opioid analgesics, that will be needed by the pain-relief services.

Policy and regulatory needs

- *Assessment and modification of policies, laws and regulations costs*. These costs are both direct and indirect. The direct costs are linked to the assessment and modification of policies and regulations; the indirect costs are linked to information dissemination to ensure that the new policies and regulations are known and applied in the country and to scale up the different levels of services. These indirect costs may partly overlap with training needs, but it is important that governments also factor these costs into their planning to improve pain management.

Similarly, cost estimates for the introduction and implementation of non-pharmacological interventions should be factored and integrated wherever possible into the health system's comprehensive planning for pain management.

4.6 Saving resources by treating pain

The burden of pain on the individual, family, community and society is often underestimated. Traditional methods for estimating the economic burden of disease, such as prevalence and incidence, are difficult to employ when determining the burden of acute and persisting pain. Moreover, these methods fail to take into account the consequences of the distressing nature of pain and its impact on daily life. Chronic pain has a major impact on labour market participation and productivity, and is often the reason why people leave the labour market prematurely. Similarly, persisting pain in children is the cause of missed days at school and parents' and caregivers' absenteeism.

Untreated pain not only affects the individual in pain, but also his or her family, the community and society as a whole. This is because pain is accompanied by other symptoms, such as depression, anxiety and physical limitations, and social isolation for patients and their siblings. The adequate management of pain through a comprehensive approach, which considers the pharmacological, physical, behavioural and spiritual dimensions, offers a solution that not only relieves pain, but also removes these hidden costs.

Thus, policy-makers should embrace a whole-system approach for the treatment of pain and make it an integral part of the national health and social system. Indeed, adequate management of pain in adults and children reduces costs for society, positively impacts on the rational utilization of health-system services, and generates both an economic and social return for the country (*103–108*).

4.7 Pain management coverage

The coverage of pain management in the health system should comprise all three levels of care: tertiary, secondary and primary. These treatment guidelines have been conceived to provide a tool to be used and adapted for these three levels of services. Pain management coverage can also be successfully extended to the community level.

Community health approaches have been adopted for palliative care, especially in contexts where the burden of palliative care could not be sustained in the primary health-care level. This approach has been adopted in countries with serious shortages of health-care providers and a high burden of disease. Given the very limited health infrastructure and resources, and the high demand for palliative-care service coverage, community and home-based care is viewed as key in responding to palliative-care needs.

Some countries have developed strong home-based care networks in coordination with the primary health-care system to respond to the HIV/AIDS epidemic, and as part of the continuum of care for cancer and other chronic conditions. Important palliative-care initiatives involve both governmental as well as nongovernmental initiatives, supported in many cases by international organizations. These initiatives have produced a solid knowledge base of how non-costly, good-quality palliative care can be provided in low resource settings. They rely mainly on networks of community members, educated and supervised by a palliative-care team (*109, 110*).

4.8 Human resources for pain management

Pain management should be provided within the available health workforce of a country's health system. Some countries are experiencing health workforce shortages and overburdened health services. Countries should consider how to use the available health workforce in a cost-effective way while introducing or expanding pain management to the community level. Each country designs and regulates its health system taking into account the composition of its health manpower (type and numbers of health professionals, level of training on analgesia, geographical distribution within the country, e.g. rural versus urban areas).

Recommendations

20. Education of health professionals in the standardized management of persisting pain in children with medical illnesses and in the handling of the necessary medicines, including opioid analgesics, is encouraged.
21. Health professionals will be allowed to handle opioids within their scope of practice or professional role based on their general professional licence without any additional licensing requirements.
22. In addition, countries may consider, subject to their situation, allowing other professions to diagnose, prescribe, administer and/or dispense opioids for reasons of flexibility, efficiency, increased coverage of services and/or improved quality of care.
23. The conditions under which such permission is granted should be based on the demonstration of competence, sufficient training, and personal accountability for professional performance. *Guidelines Development Group experts' opinion*

In the context of pain management, the delegation of tasks means that a number of activities for pain assessment and pain management are transferred from specialized doctors to other health professionals. This may include the prescription of opioid analgesics. The delegation of tasks must be implemented within systems that contain adequate checks and balances to protect both health-care providers and the people receiving treatment and care. A few countries have been changing policies and regulations to allow nurses and clinical officers to prescribe opioid medicines in order to provide service coverage for pain relief. The above recommendation was formulated by the Guidelines Development Group taking into account the published and unpublished experience in pain management in national health systems as well as the implementation and quality of care provided for other medical conditions (Annex 3. *Background to the health system recommendations*). Additional documented evidence is needed to inform policy-makers on the possible strategies to increase coverage of services while maintaining quality of care. The World Health Organization has developed a series of global recommendations for task shifting of HIV services, whose general principles can be adopted for other delegation of tasks in the health system (*111*).

These global recommendations and guidelines on task shifting have looked at the following aspects:

- the adoption of a task shifting approach as a health initiative after consideration of the human resources analysis and gaps;
- the creation of an enabling regulatory environment for its implementation (e.g. legally empowering health professionals to perform the delegated tasks);
- the assurance of quality of care and sustainability of this approach in the health system.

4.9 What treatment should be available

Evidence of effectiveness and safety in children is a prerequisite for making programmatic choices on the types of medicines and formulations to be made available for pain treatment in children. Considerations of costs, availability and feasibility of medicines also influence the choice between medicines with comparable effectiveness and safety profiles.

These guidelines cover the minimum pharmacological interventions to relieve persisting pain in children with medical illnesses. Evidence on the use of non-opioid analgesics, opioid analgesics and possible adjuvant medicines to relief pain in this specific population was retrieved and appraised. As part of this transparent and rigorous process, a research agenda for missing evidence on these pharmacological interventions was produced to guide the international scientific community in its research in this field (Annex 5. *Research agenda*).

The adoption of evidence-based guidelines provides the basis for selecting essential medicines for countries' health systems. Each country should have its own list of essential medicines. This central policy tool, inspired by the concept set out in the WHO model lists of essential medicines for adults and children, is used to plan the availability and affordability of medicines in the national pharmaceutical sector. The goal of the national essential medicines list is to provide a minimum list of the most efficacious, safe and cost-effective medicines needed for a basic health-care system in order to treat priority diseases and conditions. Priority diseases are selected on the basis of current and estimated future public health relevance for the country.

In conjunction with the development of national evidence-based guidelines for the treatment of pain, which is supported by WHO guidance, countries should ensure that medicines for pain management in children (adequate strengths and formulations) are included in their national essential medicines list and in their national essential medicines procurement processes, and health insurance schemes.

While opioids are potent medicines for the relief of moderate and severe pain, there is a risk of misuse and diversion, which can be low or high, depending on the country. Measures to reduce the risk of misuse of opioid medicines include alertness for this possibility and appropriate prescribing, including careful patient selection. To prevent accidental overdose by family members, the caregivers and the patient should be warned to store the medicines in a safe place in child-proof containers. The possibility that one of the parents may have opioid dependence and may be taking the opioids themselves should also be considered.

ANNEX 1. PHARMACOLOGICAL PROFILES

This section gives the pharmacological profiles of the non-opioid and opioid analgesic medicines for the relief of persisting pain in children with medical illnesses referred to previously in Chapter 3. It also includes the profile of naloxone, the antidote in case of opioid overdose.

The formulations and strengths in this section are indicative of medicines generally available on the market. Countries may have access to different formulations and strengths. The formulations listed are those generally marketed for persisting pain in children. For the medicines listed in the *WHO model list of essential medicines for children,* all listed formulations are included.

A1.1 Fentanyl

ATC Code: N01AH01
Transmucosal lozenge: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg (as citrate).
Transdermal patch (extended release): 12.5 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 of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

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, for example, riding a bike.

Dosage:

Starting dose for opioid-naive patients:
IV injection:
- **neonate** or **infant** – 1–2 mcg/kg per dose slowly over 3–5 minutes; repeated every 2–4 hours;
- **child** – 1–2 mcg/kg per dose, repeated every 30–60 minutes.

Continuous IV infusion:
- **neonate** or **infant** – initial IV bolus of 1–2 mcg/kg (slowly over 3–5 minutes) followed by 0.5–1 mcg/kg/hr;
- **child** – initial IV bolus of 1–2 mcg/kg (slowly over 3–5 minutes), followed by 1 mcg/kg/hr (titrate dose upward if necessary).

Continuation: after a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% under monitoring of the patient. (The usual IV dose is 1–3 mcg/kg/hr, some children require up to 5 mcg/kg/hr.)

Dose for breakthrough pain
Transmucosal lozenge (oral transmucosal fentanyl citrate or OTFC):
- **child over 2 years and over 10 kg body weight** – 15–20 mcg/kg as a single dose (maximum 400 mcg); if more than 4 doses of breakthrough pain medication are needed each day, adjust dose of background analgesic.

Dose when switching from morphine:
Transdermal patch:
- **child 2 years or over, who is opioid tolerant and on at least 45–60 mg of oral morphine equivalent per day** – use 25 mcg/hr system (or higher, based on conversion to fentanyl equivalents – see Notes); the child should have stable pain management with a short-acting opioid at least for 24 hours prior to commencing a fentanyl transdermal patch (with supplemental doses when required for breakthrough pain); then switch to a fentanyl transdermal patch; dose may be increased after three days (based on breakthrough pain needs); use a ratio of 45 mg of oral morphine equivalents per 12.5 mcg/hr increase in patch dosage (see below under equianalgesic doses). Change patch every 72 hours; a 48-hour schedule is not recommended in children.

Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week (*79, 80*).

Renal Impairment: moderate (glomerular filtration rate (GFR) 10–20ml/min or serum creatinine 300–700 micromol/l) – reduce dose by 25%; severe (GFR <10ml/min or serum creatinine >700micromol/l) – reduce dose by 50%.

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

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, depersonalisation, 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;
- **protease inhibitors** – possible enhanced or prolonged effects of fentanyl.

* Indicates severe.

Notes:
- Fentanyl is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- Other dose forms of fentanyl are available but these currently have no role in the management of paediatric persisting pain and their use has not been considered.
- Grapefruit juice should be avoided as fentanyl serum concentrations may be significantly increased.
- IV administration:
  - Administer by slow intravenous injection over 3–5 minutes or by continuous infusion.
  - The intravenous doses for neonates, infants and children are based on acute pain management and sedation dosing information; lower doses may be required in patients without ventilatory support.
- Transdermal patch:
  - Reservoir type transdermal patches should not be cut because damage to the rate-controlling membrane can lead to a rapid release of fentanyl and overdose.
  - Apply to clean, dry, non-hairy, non-irritated, intact skin on torso or upper arm; remove after 72 hours and apply replacement patch on a different area (avoid the same area for several days).
  - When patches are removed, they should be folded in half with the adhesive side facing inwards and discarded appropriately as the quantity of fentanyl remaining in the patch can be significant and enough to poison a child or animal if not disposed of properly.
  - Transdermal patches should be used with caution in cachectic children because of poor absorption.
  - Some patients experience withdrawal symptoms (e.g. diarrhoea, colic, nausea, sweating, restlessness) when changed from oral morphine to transdermal fentanyl despite satisfactory pain relief, in which case rescue doses of morphine can be used until symptoms resolve (usually a few days).

- Oral transmucosal fentanyl citrate:
  - to achieve maximum mucosal exposure to the fentanyl, the lozenge should be placed inside the mouth against the buccal mucosa and moved constantly up and down, and changed at intervals from one side to the other.
  - the lozenge should not be chewed but the aim is to consume the lozenge within 15 minutes.
- Naloxone is used as an antidote in case of opioid overdose.

Equianalgesic doses:

The following 24 hour doses of morphine by mouth are considered to be approximately equal to the fentanyl transdermal patches shown*:

- morphine salt 45 mg daily = fentanyl 12.5 mcg patch
- morphine salt 90 mg daily = fentanyl 25 mcg patch
- morphine salt 180 mg daily = fentanyl 50 mcg patch
- morphine salt 270 mg daily = fentanyl 75 mcg patch
- morphine salt 360 mg daily = fentanyl 100 mcg patch.

**This table represents a conservative conversion to fentanyl transdermal patch and should NOT be used to convert from transdermal fentanyl to other analgesic therapies; overestimation of the dose of the new agent and possibly overdose with the new analgesic agent may result. The dosing conversion above from oral morphine to transdermal fentanyl is conservative to minimize the potential for overdosing patients with the first dose, and therefore approximately 50% of patients are likely to require a higher dose following the initial application.*

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A1.2 Hydromorphone

ATC Code: N02AA03
Injection: 1 mg in 1 ml ampoule, 2 mg in 1 ml ampoule, 4 mg in 1 ml ampoule, 10 mg in 1 ml ampoule (as hydrochloride).
Tablet: 2 mg, 4 mg, 8 mg (as hydrochloride).
Oral liquid: 1 mg (as hydrochloride)/ml.

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 of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

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, for example, riding a bike.

Dosage:

Starting dose for opioid-naive patients:
Oral (using immediate-release formulations):
- child – initially 30–80 mcg/kg per dose (maximum 2 mg per dose) every 3–4 hours.

Subcutaneous or intravenous:
- child – initially 15 mcg/kg per dose slowly over at least 2–3 minutes every 3–6 hours.

Continuation: After a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient.

Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week (*79, 80*).

Renal impairment: moderate (GFR 10–20ml/min or serum creatinine 300–700 micromol/l) and severe (GFR <10ml/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, lightheadedness, 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;
- **opioid antagonists/partial agonists*** – may precipitate opioid withdrawal symptoms.

* Indicates severe.

Notes:
- Hydromorphone is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another.
- Give with food or milk to decrease gastrointestinal upset.
- Extended-release preparations are available; however, these are not indicated for use in the paediatric setting.
- Naloxone is used as an antidote in case of opioid overdose.

Equianalgesic doses:

Hydromorphone - morphine vice versa
According to manufacturers, oral hydromorphone is 7.5 times more potent than morphine; however, when switching from morphine to hydromorphone, some suggest the ratio is 5:1 (i.e. the dose of hydromorphone should be 1/5 of the morphine dose), and when switching from hydromorphone to morphine a ratio of 1:4 should be used (i.e. the morphine dose should be 4 times the hydromorphone dose).

Parenteral hydromorphone to oral hydromorphone
If switching from parenteral to oral hydromorphone, oral doses are less than one-half as effective as parenteral doses (may only be 1/5 as effective). Doses may need to be titrated up to 5 times the IV dose.

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A1.3 Ibuprofen

ATC code: M01AE01
Tablet: 200 mg, 400 mg.
Oral liquid: 40 mg/ml.

Indications: mild persisting pain.

Contraindications: hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs); active peptic ulceration or upper gastrointestinal bleeding; severe renal failure, hepatic failure or cardiac failure.

Precautions: asthma; cardiac disease; volume depletion, such as in gastroenteritis or dehydration (increased risk of renal impairment); concomitant use of drugs that increase risk of bleeding; previous peptic ulceration; coagulation defects; allergic disorders; renal impairment; hepatic impairment.

Dosage:

Oral:
- **infant over 3 months or child** – 5–10 mg/kg three or four times daily with or after food; maximum total daily dose is 40 mg/kg/day divided into 4 doses.

Renal impairment: mild (GFR 20–50 ml/min or approximate serum creatinine 150–300 micromol/l) – use lowest effective dose and monitor renal function; sodium and water retention may occur as may deterioration in renal function, possibly leading to renal failure; moderate (GFR 10–20ml/min or serum creatinine 300–700 micromol/l) to severe (GFR <10ml/min or serum creatinine >700 micromol/l) – avoid.

Hepatic impairment: use with caution, there is an increased risk of gastrointestinal bleeding; can cause fluid retention; avoid in severe liver disease.

Adverse effects:
- **common** – nausea, diarrhoea, dyspepsia, headache, abdominal pain, anorexia, constipation, stomatitis, flatulence, dizziness, fluid retention, raised blood pressure, rash, gastrointestinal ulceration and bleeding;
- **uncommon** – urticaria, photosensitivity, anaphylactic reactions, renal impairment;
- **rare** – angioedema, bronchospasm, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

Interactions with other medicines:
- **acetylsalicylic acid and other NSAIDs*** – avoid concomitant use (increased adverse effects);
- **cyclosporin*** – increased risk of nephrotoxicity;
- **dexamethasone** – increased risk of gastrointestinal bleeding and ulceration;
- **digoxin** – possibly exacerbation of heart failure, reduced renal function and increased plasma digoxin concentration;
- **enalapril** – antagonism of hypotensive effect, increased risk of renal impairment;
- **fluoxetine*** – increased risk of bleeding;

- **furosemide** – risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect;
- **heparin** – possibly increased risk of bleeding;
- **hydrocortisone** – increased risk of gastrointestinal bleeding and ulceration;
- **levofloxacin*** – possibly increased risk of convulsions;
- **lithium*** – reduced excretion of lithium (increased risk of toxicity);
- **methotrexate*** – excretion of methotrexate reduced (increased risk of toxicity);
- **ofloxacin*** – possible increased risk of convulsions;
- **penicillamine** – possible increased risk of nephrotoxicity;
- **phenytoin*** – effect of phenytoin possibly enhanced;
- **prednisolone** – increased risk of gastrointestinal bleeding and ulceration;
- **propranolol** – antagonism of hypotensive effect;
- **ritonavir** – possible increased plasma concentration;
- **spironolactone** – risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia;
- **warfarin*** – anticoagulant effect possibly enhanced; higher risk of intestinal bleeding;
- **zidovudine** – increased risk of haematological toxicity.

*Indicates severe.

Notes:

- Administer with or after food.
- Age restriction: > 3 months.

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A1.4 Methadone

ATC Code: N07BC02
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 only be commenced 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 of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

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 (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 or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike.

Dosage:

Starting dose for opioid-naive patients:
Oral, subcutaneous or intravenous:

- **child** – initially 100–200 mcg /kg every 4 hours for the first 2–3 doses, then 100–200 mcg /kg every 6–12 hours; maximum of 5 mg per dose initially. Administer IV methadone slowly over 3–5 minutes.

Continuation: After a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient. Then, the dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation. From then on dosage increases should be performed at intervals of one week or over and with a maximum increase of 50% (see Notes for important information regarding dose titration).

Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week (*79, 80*).

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, dyshporia, dependence, confusion, urinary retention, ureteric spasm;
- **uncommon** – restlessness, dyspnoea, hypoventilation, depersonalisation, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, muscle weakness, hypertension, dizziness, itching, bronchospasm, dysmenorrhoea, dry eyes, hyperprolactinaemia;
- **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;
- **zidovudine** – methadone possibly increases zidovudine concentration.

* Indicates severe.

Notes:

- Methadone is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- The dosage should be titrated clinically with close observation of the patient. Because of the large volume of distribution, higher doses are required for the first few days while the body tissues become saturated; once saturation is complete, a smaller daily dose will be sufficient. Continuing on the initial daily dose is likely to result in sedation within a few days, possibly respiratory depression, and even death.
- Administer with juice or water.
- Dispersible tablet should be completely dissolved before administration.
- Methadone has a long and variable half-life and potentially lethal drug interactions with other drugs.

- Care needs to be taken with methadone to avoid toxicity because the time to reach steady state concentrations following a change in dosage may be up to 12 days.
- Particular attention is required during initiation of treatment, during conversion from one opioid to another and during dose titration.
- Prolongation of the QT interval or torsade de pointes (especially at high doses) may occur.
- Use with caution as methadone's effect on respiration lasts longer than analgesic effects.
- Naloxone is used as an antidote in case of opioid overdose.
- As methadone has a long half-life, infusion of naloxone may be required to treat opioid overdose.

Equianalgesic doses:

Dose conversion ratios from other opioids are not static but are a function of previous opioid exposure, and are highly variable.

Published tables of equianalgesic doses of opioids, established in healthy non-opioid tolerant individuals, indicate that methadone is 1–2 times as potent as morphine in single dose studies, but in individuals on long-term (and high dose) morphine, methadone is closer to 10 times as potent as morphine; it can be 30 times more potent or occasionally even more. The potency ratio tends to increase as the dose of morphine increases. If considering methadone, thought should be given to the potential difficulty of subsequently switching from methadone to another opioid.

Other opioids should be considered first if switching from morphine due to unacceptable effects or inadequate analgesia. Consultation with a pain clinic or palliative-care service is advised.

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A1.5 Morphine

ATC code: N02AA01
Oral liquid: 2 mg (as hydrochloride or sulfate)/ml.
Tablet: 10 mg (as sulfate).
Tablet (prolonged release): 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (as sulfate).
Granules: (prolonged release, to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).
Injection: 10 mg (as hydrochloride or sulfate) in 1 ml ampoule.

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 of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

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 carer about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike.

Dosage:

Starting dose for opioid-naive patients:
Oral (immediate-release formulation):
- **infant 1–12 months** – 80–200 mcg/kg every 4 hours;
- **child 1–2 years** – 200–400 mcg/kg every 4 hours;
- **child 2–12 years** – 200–500 mcg/kg every 4 hours; maximum oral starting dose is 5 mg.

Oral (prolonged-release formulation):
- **child 1–12 years** – initially 200–800 mcg/kg every 12 hours.

Subcutaneous injection:
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant** or **child 6 months–2 years** –100 mcg/kg every 4 hours;
- **child 2–12 years** – 100–200 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

IV injection over at least 5 minutes:
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant** or **child 6 months–12 years** – 100 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

IV injection and infusion:
- **neonate** – initially by *intravenous injection* over at least 5 minutes 25–50 mcg/kg, followed by continuous intravenous infusion 5–10 mcg/kg/hr;
- **infant 1–6 months** – initially by *intravenous injection* over at least 5 minutes 100 mcg/kg, followed by *continuous intravenous infusion* 10–30 mcg/kg/hr;
- **infant** or **child 6 months–12 years** – initially by *intravenous injection* over at least 5 minutes 100–200 mcg/kg followed by *continuous intravenous infusion* 20–30 mcg/kg/hr.

Continuous SC infusion:
- **infant 1–3 months** – 10 mcg/kg/hr;
- **infant** or **child 3 months–12 years** – 20 mcg/kg/hr.

Continuation: After a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient.

Dose for breakthrough pain

Oral (immediate-release formulation), IV injection, or subcutaneous:

- Additional morphine may be administered as frequently as required with a maximum of 5–10% of the regular daily baseline morphine dose. If repeated breakthrough doses are required, adjust the regular baseline morphine dose guided by the amount of morphine required for breakthrough pain with a maximum increase of 50% per 24 hours.

Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week (*79, 80*).

Renal impairment: mild (GRF 20–50 ml/min or approximate serum creatinine 150–300 micromol/l) to moderate (GFR 10–20 ml/min or serum creatinine 300–700 micromol/l) – reduce dose by 25%; severe (GFR <10 ml/min or serum creatinine >700 micromol/l) – reduce dose by 50% or consider switching to alternative opioid analgesics which have less renal elimination, such as methadone and fentanyl; increased and prolonged effect; increased neurotoxicity.

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

Adverse effects:

- **common** – nausea, vomiting, constipation, lightheadedness, drowsiness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, palpitation, bradycardia, postural hypotension, miosis;
- **uncommon** – respiratory depression (dose-related), tachycardia, palpitations;
- **rare** – syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

Interactions with other medicines*:

- **amitriptyline** – possibly increased sedation, and it may increase plasma concentration of morphine;
- **chlorpromazine** – enhanced sedative and hypotensive effect;
- **ciprofloxacin** – manufacturer of ciprofloxacin advises that premedication with morphine (reduced plasma ciprofloxacin concentration) be avoided when ciprofloxacin is used for surgical prophylaxis;
- **diazepam** – enhanced sedative effect;
- **haloperidol** – enhanced sedative and hypotensive effect;
- **metoclopramide** – antagonism of effect of metoclopramide on gastrointestinal activity;
- **naloxone*** – precipitates opioid withdrawal symptoms;
- **naltrexone*** – precipitates opioid withdrawal symptoms;
- **opioid antagonists/partial agonists** – may precipitate opioid withdrawal symptoms;
- **ritonavir*** – possibly increases plasma concentration of morphine.

* Indicates severe.

Notes:

- Morphine is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- Prolonged-release morphine preparations must not be crushed or chewed; the child must be able to swallow the whole tablet; alternatively, prolonged-release granules can be used.
- Subcutaneous injection is not suitable for oedematous patients.
- For continuous intravenous infusion, dilute with glucose 5% or 10% or sodium chloride 0.9%.
- High strength modified-release tablets and capsules should only be used in patients who are opioid tolerant. Administration of these strengths to non-opioid tolerant patients may cause fatal respiratory depression.
- Naloxone is used as an antidote in case of opioid overdose.

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A1.6 Naloxone

ATC code: V03AB15
Injection: 400 mcg/ml (hydrochloride) in 1 ml ampoule.

Indications: opioid overdose.

Contraindications: there are no contraindications to the use of naloxone for treatment of opioid toxicity.

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

Dosage:

Dose in opioid-tolerant patients
Intravenous:

- **neonate, infant** or **child** – 1 mcg/kg titrated over time, e.g. every 3 minutes, until the child is breathing spontaneously and maintaining adequate oxygenation; a low dose infusion may be required thereafter to maintain adequate respiration and level of consciousness until the effect of overdose has resolved; close monitoring is needed.

Dose in opioid-naive patients

Intravenous:

- **neonate, infant** or **child** – 10 mcg/kg; if no response, give subsequent dose of 100 mcg/kg (resuscitation doses); review diagnosis if respiratory function does not improve; further doses may be required if respiratory function deteriorates.

Continuous IV infusion using an infusion pump:

- **neonate, infant** or **child** – 5–20 mcg/kg/hr, adjusted according to response.

Renal impairment: excretion of some opiods 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.

Notes:

- Naloxone hydrochloride may be administered in the same doses as for intravenous injection by subcutaneous injection, but only if the intravenous route is not feasible (slower onset of action).
- For continuous intravenous infusion, dilute to a concentration of 4 mcg/ml with glucose 5% or sodium chloride 0.9%.
- For intravenous bolus, administer over 30 seconds as undiluted preparation.
- The intravenous dose may be repeated every 2–3 minutes until response.
- After initial response, the intravenous dose may need to be repeated every 20–60 minutes due to the short duration of action.
- Do not administer naloxone to neonates of mothers who have been taking methadone or heroin.

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A1.7 Oxycodone

ATC Code: N02AA05
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 of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

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, for example, riding a bike.

Dosage:

Starting dose for opioid-naive patients:
Oral (immediate-release formulation):
- **infant 1–12 months** – 50–125 mcg/kg every 4 hours;
- **child 1–12 years** – 125–200 mcg/kg every 4 hours, max 5 mg.

Oral (prolonged-release formulation):
- **child over 8 years** – 5 mg every 12 hours.

Continuation: After a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with careful monitoring of the patient.

Dose for breakthrough pain
Oral (using immediate-release preparation):
- **infant** or **child**: Additional oxycodone may be administered as frequently as required with a maximum of 5–10% of the regular daily baseline oxycodone dose. If repeated breakthrough doses are required, adjust the regular baseline oxycodone dose guided by the amount of oxycodone required for breakthrough pain with a maximum increase of 50% per 24 hours.

Dosage discontinuation: for short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval. In the case of a long-term therapy protocol, the dose should be reduced not more than 10–20% per week (*79, 80*).

Renal impairment: mild (GRF 20–50 ml/min or approximate serum creatinine 150–300 micromol/l) to severe (GFR <10ml/min or serum creatinine >700micromol/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;
- **opioid antagonists/partial agonists*** – may precipitate opioid withdrawal symptoms.

* Indicates severe.

Notes:

- Oxycodone is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- Prolonged-release oxycodone preparations must not be crushed or chewed; the child must be able to swallow the whole tablet.
- To administer with food to reduce gastrointestinal upset.
- Oxycodone is partially metabolized to an active metabolite, oxymorphone, via CYP2D6 pathway; slow or ultra-fast metabolizers may experience reduced or enhanced analgesia and dose-related side-effects.
- High strength modified-release tablets should only be used in patients who are opioid tolerant. Administration of these strengths to non-opioid tolerant patients may cause fatal respiratory depression.
- Naloxone is used as an antidote in case of opioid overdose.

Equianalgesic doses:

When converting from oral morphine to oral oxycodone, use an initial dose conversion ratio of 1.5:1 (e.g. replace 15 mg morphine with 10 mg oxycodone). Then titrate to optimize the analgesia.

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A1.8 Paracetamol

ATC code: N02BE01
Oral liquid: 25 mg/ml.
Suppository: 100 mg.
Tablet: 100–500 mg.
also referred to as acetaminophen.

Indications: mild pain.

Precautions: hepatic impairment, renal impairment, overdose.

Dose:

Oral or rectal:
- **neonate** – 10 mg/kg every 6–8 hours as necessary; maximum dose is 4 doses in 24 hours;
- **infant** or **child** – 15 mg/kg, up to 1 g, every 4–6 hours as necessary; maximum dose is 4 doses, or 4 g, in 24 hours.

Hepatic impairment: dose-related toxicity; do not exceed the daily recommended dose.

Adverse effects:
- **rare** – rash, pruritus, urticaria, hypersensitivity, anaphylactic reactions, neutropenia, thrombocytopenia, pancytopenia.
  Hepatotoxicity (and less frequently renal damage) can occur after paracetamol overdose and can even occur at standard doses in children with the conditions described above.

Interactions with other medicines:
- **carbamazepine** – increased potential hepatotoxicity to paracetamol;
- **metoclopramide** – increased absorption of paracetamol;
- **phenobarbital** – increased potential hepatotoxicity to paracetamol;
- **phenytoin** – increased potential hepatotoxicity to paracetamol;
- **warfarin** – prolonged regular use of paracetamol possibly enhances anticoagulant effect.

Notes:

- Infants under 3 months should not be given paracetamol unless advised by a doctor.
- Shake suspension well before use and use a measuring device provided with the formulation.
- Children may be at an increased risk of liver damage from paracetamol overdose if they are malnourished, obese, suffering from febrile illness, taking a prolonged course of treatment, have poor oral intake (nutrition and hydration), or are taking liver enzyme inducing drugs.
- Acetylcysteine is used as an antidote in case of overdose.

References:

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http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf, accessed 19 January 2011).

ANNEX 2. BACKGROUND TO THE CLINICAL RECOMMENDATIONS

This annex reports the detailed considerations by the WHO Guidelines Development Group for each recommendation as mentioned in Chapter 3. ***Pharmacological treatment strategies.*** They were formulated at a meeting held at the Rockefeller Conference Center in Bellagio, Italy, in March 2010. These recommendations arise from an appraisal of the evidence retrieved and reported in Annex 4. ***Evidence retrieval and appraisal,*** and additional evidence and considerations such as the balance between benefits and risks, values, acceptability, feasibility and costs of the interventions.

A2.1 Development process

These guidelines were developed in accordance with the principles and procedures laid down by the WHO Guidelines Review Committee (GRC), which was established in 2007 to ensure WHO guidelines are consistent with internationally accepted best practices, including the appropriate use of evidence. The present *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses* were prepared according to the *WHO handbook for guideline development* and modified as necessary to provide advice on many complex clinical questions in children for which evidence is either extremely limited or nonexistent (*112*).

An Expanded Review Panel (ERP) for the WHO pain guidelines, composed of international scientists and experts in pain management, formulated the clinical and health system questions to be addressed in the preparation of the guidelines. The document containing the questions and describing the planned content of the guidelines is referred to as the *Scoping document for the WHO treatment guidelines for chronic pain in children* (*113*).

Detailed searches were undertaken on these questions to identify, in order of priority, systematic reviews of randomized control trials (RCTs) and of observational studies on persisting pain in children. The evidence retrieved was subsequently reviewed by the ERP for completeness. During a third step, additional studies provided by the ERP were screened for relevance, scope and study design in order to include them among the studies retrieved in the initial search. For those interventions where neither systematic reviews nor RCTs were retrieved, the ERP and the WHO Expert Panel on Drug Evaluation were requested to provide observational studies (preferably cohort studies and case-control) and pharmacokinetics studies, which could inform a discussion on these interventions.

Once this process was concluded, the Guidelines Development Group (GDG), a subgroup of the Expanded Review Panel comprised of an international multidisciplinary group of experts on pain management, convened in March 2010 to assess the evidence and formulate recommendations, define a research agenda, and review and contribute to the development of the chapters in the guidelines.

The quality of the evidence was assessed and classified according to the methodology described by the GRADE working group (Box 0.1 in the Introduction section, above) (*114*). The GRADE profiles and the classification of the retrieved evidence are presented in Annex 4. *Evidence retrieval and appraisal.*

The recommendations were formulated taking into account not only the quality of the evidence but also a number of other considerations, including the balance between risks and benefits, the feasibility and cost of the interventions, and ethical considerations and their impact on policy. The Guidelines Development Group formulated the recommendations after analysing and discussing these issues and arriving at a consensus on the text and strength of the recommendations. No differences of opinion remained unresolved, which obviated the need to vote on individual preferences for any of the recommendations.

The recommendations are termed as "strong" or "weak" and should be interpreted by patients, clinicians and policy-makers as outlined in Box 0.2 (in the Introduction section, above). The recommendations formulated on clinical interventions constitute the backbone of the pharmacological treatment chapter and provide guidance to health-care providers. Documentation on the issues taken into consideration by the GDG when formulating the recommendations can be found in Annex 2. *Background to the clinical recommendations*. The aim was to ensure maximum transparency of the rationale for the recommendations and supporting evidence.

A2.2 Pharmacological interventions

A2.2.1 A two-step approach versus the three-step ladder

Clinical question

In children with persisting pain due to medical illnesses, what is the evidence for using a two-step analgesic ladder versus a three-step analgesic ladder for rapid effective and safe pain control? If the evidence supports the use of a three-step ladder, should codeine as compared to tramadol be used at step two?

Recommendation

1. It is recommended to use the analgesic treatment in two steps according to the child's level of pain severity.
   Strong recommendation, very low quality of evidence

Domains and considerations

Quality of evidence

There are no formal comparisons between two-step and three-step treatment in children. The two potential medicines that might appear in the second step present challenges in children.
Tramadol is generally not registered for use in children below the age of 12 years, as evidence of efficacy and safety is not available, and has not been submitted for evaluation by medicines regulatory agencies.
Codeine presents well-known safety and efficacy difficulties related to genetic variability in biotransformation (CYP2D6), although it is registered for use and has been widely used in children.
Uncertainty: yes, for the three-step pharmacological pain treatment approach.

Risks/benefits

Benefits

The potential benefit of having access to effective opioid analgesics outweighs the benefits of codeine in this age group.

Risks

The risks associated with strong opioids are recognized, but are acceptable in comparison to the uncertainty associated with codeine and tramadol.

Uncertainty: if there is new evidence for tramadol or an alternative intermediate potency opioid, then this benefit-risk assessment can be reconsidered.

Values and acceptability

In favour

The panel placed high value on effective treatment of pain.

Against

The panel acknowledged continuing barriers to access to strong opioids in many settings, but a strong recommendation in this regard could overcome this negative sentiment and promote wider access to opioids for pain relief.

Uncertainty: none.

Cost

Although tramadol is now off patent in many markets and generics have been launched, the problem of market authorization for children remains in several countries. Codeine is widely available and inexpensive, but presents potential lack of efficacy and/or safety problems in an unpredictable proportion of patients. Although access to strong opioids is variable, price is not generally a significant barrier.

Uncertainty: none.

Feasibility

Child-appropriate dosage forms for opioids are available with the exception of very young infants. Liquid preparations allow for easier dose titration, but concern about cost, stability, portability and storage remain.

The dosage forms reported in the 2010 EMLc are as follows:

- **granules:** modified release (to mix with water), 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
- **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, 100 mg, 200 mg (morphine sulfate).

Strong opioids are not available in all countries.

Uncertainty: none.

Research agenda

1. Research on potential alternatives to codeine as a second step in a three-step approach is needed.
2. Long-term safety data of non-steroidal anti-inflammatory drugs and paracetamol is needed.

A2.2.2 Paracetamol versus non-steroidal anti-inflammatory drugs

Clinical question

In children with persisting pain due to medical illnesses, should paracetamol as compared to NSAIDs be used at step one of a two- or three-step approach?

Recommendations

2. Paracetamol and ibuprofen are the medicines of choice in the first step (mild pain).
   - The panel opted not to recommend either paracetamol or ibuprofen in preference to one another. Both these medicines have a place in the first step of the two-step analgesic approach.
3. Both paracetamol and ibuprofen need to be made available for treatment in the first step.
   Strong recommendations, low quality of evidence

Domains and considerations

Quality of evidence

There is evidence for the superiority of the analgesic properties of ibuprofen versus paracetamol but only for acute pain (Annex 4. *Evidence retrieval and appraisal*, GRADE Table 1A and other studies in Annex 4 comparing paracetamol versus ibuprofen). This was considered low-quality evidence based on the indirectness of the condition treated and the absence of long-term safety evidence. No evidence for the safety and efficacy of other NSAIDs other than ibuprofen was found.
Uncertainty: yes, due to the lack of comparative long-term safety data.

Risks/benefits

Benefits

The panel recognized the widely-held clinical view that NSAIDs and paracetamol are indicated in different pain conditions. However, no direct evidence for this approach was identified or retrieved.

Risks

The long-term safety of both paracetamol and NSAIDs in children is unknown. There are concerns about potential renal and gastrointestinal toxicity and bleeding with NSAIDs. There are well-described risks of acute overdose associated with paracetamol. There is age restriction in the use of ibuprofen below three months of age.

Uncertainty: yes, in relation to long-term safety data and to comparative safety data with NSAIDs other than ibuprofen.

Values and acceptability

In favour

The panel places high value on having the two alternatives (paracetamol and ibuprofen).

Against

None.

Uncertainty: none.

Cost

Both paracetamol and ibuprofen are widely available and relatively inexpensive. Child-appropriate dosage forms – such as liquid oral forms – exist, but divisible dispersible oral solid dosage forms are still needed.

Uncertainty: none.

Feasibility
No problem with feasibility is anticipated.
Uncertainty: none.

Policy and research agenda
Child-appropriate dosage forms exist for both paracetamol and ibuprofen, but the development of divisible dispersible oral solid dosage forms should be prioritized.
Long-term safety data for NSAIDs and paracetamol in the paediatric population are needed.

A2.2.3 Strong opioids essential in pain treatment

Clinical question
In children with persisting pain due to medical illnesses, what are the benefits as compared to the risks (hastening death, developing dependence, respiratory depression, influencing the child's development) of taking regular or intermittent morphine for pain control as compared with a similar group of patients with persisting pain not taking any opioid analgesics?

Recommendation
4. The use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses.
   Strong recommendation, low quality of evidence

Domains and considerations

Quality of evidence
Although, no systematic reviews or randomized control trials were retrieved to guide determination of the balance between the benefits and disadvantages of the use of strong opioids in children, the panel considered indirect evidence from adult chronic non-cancer pain (*71*).
The panel noted the following statement, which supported the inclusion of morphine in the 2010 EMLc: "Morphine is the strong opioid of choice in moderate to severe pain in children and this is confirmed by a number of consensus guidelines. There is extensive clinical experience of its use in children and its use should be promoted to ensure adequate analgesia as necessary" (*72*).
Uncertainty: none.

Risks/benefits
Benefits
The efficacy of strong opioids in the relief of pain is well accepted. The panel noted, however, that studies comparing opioids are possible in this age group provided that acceptable and appropriate trial methodology is used.
Risks
Risks associated with severe side-effects and mortality arising from medication errors were considered manageable, although more data on long-term use in children are necessary.
Uncertainty: none.

Values and acceptability
In favour
The panel valued access to effective treatment of pain in children.
Against
None
Uncertainty: none.

Cost
Although access to strong opioids is variable, price is not generally a significant barrier for a number of strong opioids.
Uncertainty: none.

Feasibility
Access to strong opioids for medical use remains a challenge worldwide. However, the rational use of opioid analgesics in countries with limited financial and human resources is feasible and recommended.
Uncertainty: none.

Policy agenda
Countries should review, and if necessary, revise their policies and regulations to ensure availability and accessibility of opioid analgesics for the relief of moderate to severe pain in children as provided for in the preamble of the Single Convention on Narcotic Drugs, 1961.

A2.2.4 Choice of strong opioids

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence to support the use of morphine as a gold standard for strong opioids as compared to the use of other strong opioids (in particular fentanyl, hydromophone, oxycodone and methadone) in order to achieve rapid, effective and safe pain control?

Recommendations
5. Morphine is recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses.
6. There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.
7. Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability, including patient-related factors.
Strong recommendations, low quality of evidence

Domains and considerations

Quality of evidence
The panel noted that morphine has been available for a considerable amount of time and that high quality of evidence is unlikely to be available. The second recommendation was based on comparisons between different opioids and routes of administration in acute pain and post-operative pain in children. (Annex 4. *Evidence retrieval and appraisal*, GRADE tables 2–4, 6, 7). The assessed level of quality of evidence was downgraded because of the differences in conditions treated and duration of treatment.
Uncertainty: yes.

Risks/benefits
Benefits
Morphine is well established as first-line strong opioid.
Risks
Risks are well described and considered to be manageable.
Uncertainty: no, for the use of morphine as a first-line opioid analgesic; yes, in relation to the comparative safety and efficacy of different opioids.

Values and acceptability
In favour
The panel valued access to effective treatment.
Against
None
Uncertainty: none.

Cost
Morphine is relatively inexpensive, although prolonged-release oral solid forms are more costly.
Uncertainty: none.

Feasibility
A wide range of morphine formulations have been already included in the 2010 EMLc:
- **granules, modified release** (to mix with water) – 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
- **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, 100 mg, 200 mg (morphine sulfate).

Uncertainty: none.

Research agenda
Comparative trials of strong opioids, including fentanyl, hydromorphone, oxycodone and methadone, in the treatment of persisting moderate to severe pain in children of all ages with medical illnesses are needed. They should investigate effectiveness, side-effects and feasibility of use in this population.
Child appropriate oral solid dosage forms are needed.

A2.2.5 Prolonged-release versus immediate-release morphine

Clinical question

In children with persisting pain due to medical illnesses, should prolonged-release morphine be used in preference to immediate-release morphine to achieve and maintain effective and safe pain control?

Recommendations

8. It is strongly recommended that immediate-release oral morphine formulations be available for the treatment of persistent pain in children with medical illnesses.

9. It is also recommended that child-appropriate prolonged-release oral dosage forms be available, if affordable.
   Strong recommendations, low quality of evidence

Domains and considerations

Quality of evidence

There is insufficient evidence to support the use of prolonged-release over immediate-release morphine as a sole agent. The only available evidence is in adults (Annex 4. *Evidence retrieval and appraisal*, GRADE Table 10). The Cochrane review found that, in spite of the relevance of this comparison, only 15 studies of 460 participants compared prolonged-release morphine preparations with immediate-release morphine (*115*). None of the trials were large, having a median size of 27 participants (age range: 16–73). The results of these trials show that immediate-release and modified-release morphine formulations are equivalent for pain relief. Approximately 6% of participants (adults) in the studies who received morphine (any type) experienced intolerable adverse effects.

Uncertainty: yes, in relation to children since no studies are available in this age group.

Risks/benefits

Benefits

Immediate-release oral morphine needs to be administered more frequently, but it is always necessary in the management of episodic or breakthrough pain.

Risks

Adherence to long-term treatment with immediate-release oral morphine may be problematic.

Uncertainty: none.

Values and acceptability

In favour

The panel valued access to immediate-release oral morphine and noted that commercially marketed prolonged-release oral morphine formulations are sometimes the only products available for procurement.

Against

None

Uncertainty: none.

Cost
Immediate-release oral morphine is relatively inexpensive but may not be commercially available in all countries. Morphine powder for extemporaneous preparation may be available, but requires access to pharmacists and suitable diluents, and its compounding may be subject to legal restrictions. The stability of such preparations needs to be investigated.
Uncertainty: none.

Feasibility
No problem of feasibility, rather affordability for prolonged-release morphine formulation.
Uncertainty: none.

Research agenda
Research into appropriate formulations for the extemporaneous preparation of oral liquid morphine is needed. Dissemination of available evidence on the preparation of stable extemporaneous formulations is encouraged.

A2.2.6 Opioid rotation and opioid switching

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence to support opioid rotation policies to prevent dose escalation and side-effects?

Recommendations
10. Switching opioids and/or route of administration in children is strongly recommended in the presence of inadequate analgesic effect with intolerable side-effects.
11. Alternative opioids and/or dosage forms as an alternative to oral morphine should be available to practitioners, in addition to morphine, if possible.
12. Routine rotation of opioids is not recommended.
Strong recommendations, low quality of evidence

Domains and considerations

Quality of evidence
No systematic reviews or randomized control trials were found in children. A Cochrane Review exclusively looked for and found no RCTs on opioid switching or rotation in adults and children. Identified case reports, uncontrolled and retrospective studies were examined in order to determine the current level of evidence (*116*). The review concluded that although for patients suffering chronic cancer pain opioid switching may be the only option for enhancing pain relief and minimizing opioid toxicity, there is a current lack of an evidence base for this therapeutic strategy. A systematic review published in 2006 (*117*), identified one retrospective study of opioid switching in 22 children with cancer pain. This review described a positive response to switching in patients intolerant to a particular opioid, but noted that RCTs are lacking and that the observations were based on uncontrolled data.
Uncertainty: yes, in relation to the potential utility of rotation policies; no, in relation to switching of opioid and/or route of administration in the presence of inadequate effect or intolerable side-effects.

Risks/benefits
Benefits
The panel placed a high value on effective use of adequate doses of the chosen opioid.
Risks
Risks are well described and considered to be manageable. Access to age-appropriate dose conversion table for different opioids is necessary for safe switching.
Uncertainty: none.

Values and acceptability
In favour
The panel placed high value on treating rather than not treating pain and providing an alternative when response is inadequate and side-effects are intolerable.
Against
None
Uncertainty: none.

Cost
Alternative opioids to morphine might be more expensive. However, there are regional variations in costs and some alternatives to morphine may even be cheaper.
Uncertainty: none.

Feasibility
Access to an age-appropriate dose conversion table for different opioids is necessary for safe switching.
Uncertainty: yes.

Policy and research agenda
The panel requests an update of the 2004 Cochrane review on opioid switching, including data from children, if available. Opioid rotation policies lend themselves to investigation by prospective trials. Such research is encouraged. Research on dose conversion in different age groups is necessary.

A2.2.7 Routes of administration

Clinical question
In children with persisting pain due to medical illnesses, should the intravenous, subcutaneous, intramuscular, transdermal, rectal, intranasal routes be used in preference to the oral route for effective and safe pain control?

Recommendations
13. Oral administration of opioids is the recommended route of administration.
14. The choice of alternative routes of administration when the oral route is not available should be based on clinical judgement, availability, feasibility and patient preference.
15. The intramuscular route of administration is to be avoided in children.
Strong recommendations, very low quality of evidence

Domains and considerations

Quality of evidence
The panel based its recommendation against the intramuscular route on the value judgement that pain should not be inflicted in the administration of a medicine. There is inadequate evidence to support a preference for routes of administration other than the oral (Annex 4. *Evidence retrieval and appraisal,* GRADE tables 11–15 and other studies on strong opioids reported on in Annex 4, Section A4.3). The available studies dealt with management of acute or post-operative pain and did not provide conclusive evidence to guide recommendations.
Uncertainty: yes.

Risks/benefits
Benefits
The oral route of administration is usually the least expensive and most convenient. The subcutaneous route (via continuous infusion or intermittent bolus through an indwelling catheter) is widely used.
Risks
The intramuscular route causes unnecessary pain.
Uncertainty: none.

Values and acceptability
In favour
The panel recognizes that some patients may not be able to take oral medication, and other routes are required.
Against
Intramuscular administration is considered unacceptable, as alternatives exist.
Uncertainty: none.

Cost
Oral medications are normally less expensive than other routes of administration. Patient-controlled analgesia techniques sometimes require access to expensive equipment.
Uncertainty: none.

Feasibility
The feasibility of employing different routes of administration depends on the setting.
Uncertainty: yes.

Research agenda
Trials on the safety and efficacy of different routes of administration of opioids are needed.

A2.2.8 Breakthrough pain

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence for the benefit of using immediate-release morphine (in addition to regular background analgesia), in preference to other strong opioids and routes of administration for breakthrough pain?

Recommendations

16. A careful distinction between end-of-dose pain episodes, incident pain related to movement or procedure, and breakthrough pain is needed.
17. It is strongly recommended that children with persisting pain receive regular medication to control pain and also appropriate medicines for breakthrough pain.
    Strong recommendations, very low quality of evidence

There is insufficient evidence to recommend a particular opioid or route of administration for breakthrough pain in children. There is a need to make an appropriate choice of treatment modality based on clinical judgement, availability, pharmacological considerations and patient-related factors.

Domains and considerations

Quality of evidence
The panel noted that alternative formulations of opioids given by alternative routes of administration have been investigated for breakthrough pain in adults, but at present there are no data to support their use in children.
Uncertainty: yes.

Risks/benefits
Benefits
Unknown
Risks
The risk of high potency opioids via alternative routes of administration has not been investigated in children with persisting pain.
Uncertainty: yes.

Values and acceptability
In favour
It is important that children with persisting pain receive regular medication to control pain, and are afforded an appropriate strategy for breakthrough pain.
Against
None.
Uncertainty: none.

Cost
New formulations using alternative routes of administration to oral are expected to be more costly.
Uncertainty: yes.

Feasibility
Unknown.
Uncertainty: yes.

Research agenda
Research regarding the optimal choice of opioids and routes of administration for rapidly effective relief of breakthrough pain is needed.

A2.2.9 Adjuvant medications: steroids

Clinical question
In children with persisting pain due to medical illnesses, should corticosteroids as an adjuvant medication be used as compared to placebo in order to achieve and maintain effective and safe pain control?

Recommendation
18. The use of corticosteroids is **not** recommended in the treatment of persisting pain in children with medical illnesses as adjuvant medicines.
Weak recommendation, very low quality of evidence

Domains and considerations

Quality of evidence
Corticosteroids are indicated in the management of specific conditions, such as for the reduction of peritumour oedema, for raised intracranial pressure in central nervous system tumours, and for the treatment of neuropathic pain due to spinal cord compression. No studies in children were retrieved on corticosteroids as an adjuvant in pain relief.
Uncertainty: yes.

Risks/benefits
Benefits
No known benefits outside of specific indications.
Risks
Corticosteroids are identified with well-known adverse effects, particularly with chronic use.
Uncertainty: none.

Research agenda
No research need identified.

A2.2.10 Adjuvants in bone pain: bisphosphonates

Clinical question
In children with bone pain related to medical illnesses, what is the evidence for the use of bisphosphonates as an adjuvant medication in order to achieve and maintain effective and safe pain control?

Recommendations
19. The use of bisphosphonates as adjuvant medicines is **not** recommended in the treatment of bone pain in children.
Weak recommendation, very weak quality of evidence

Domains and considerations

Quality of evidence
No systematic reviews, RCTs or other studies on the use of bisphosphonates in the treatment of bone pain in children were identified. In adults, one systematic review suggests that that bisphosphonates provide modest pain relief for patients with painful bony metastases (*82*).
Uncertainty: yes.

Risks/benefits
Benefits
Unknown.
Risks
The risk of potentially devastating adverse effects, such as osteonecrosis of the jaw, cannot be discounted.
Uncertainty: yes.

Research agenda
Trials in children concerning the safety and the efficacy of bisphosphonates as adjuvants in the treatment of bone pain are needed.

A2.2.11 Adjuvants in neuropathic pain: antidepressants

Clinical question
In children with persisting neuropathic pain, what is the evidence for the use of amitryptiline and other tricyclic antidepressants as compared to selective serotonin reuptake inhibitors in order to achieve rapid, effective and safe pain control?

Recommendation
At present, it is not possible to make a recommendation for or against the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) as adjuvant medicines in the treatment of neuropathic pain in children.

Domains and considerations

Quality of evidence
Clinical experience and trial data in adults support the use of tricyclic antidepressants, such as amitriptyline or nortriptyline and serotonin and norepinephrine reuptake inhibitors, in the treatment of neuropathic pain (*83*). There is limited evidence to suggest that the newer SSRIs may be effective for neuropathic pain treatment in adults (*83*). There is no evidence for use of antidepressants for the management of pain in children. There is large clinical experience with the use of amitriptyline for pain management in children.
Uncertainty: yes.

Risks/benefits
Benefits
Unknown.
Risks
The general risks associated with overdose of tricyclic antidepressants are well described. The use of selective serotonin reuptake inhibitors in children and adolescents with depression has been associated with an increased risk of suicidal ideation and behaviour, although this risk has not been evaluated in adequately designed studies to measure suicide as an outcome and to measure whether SSRIs would modify the risk of suicide completion (*84*). Fluoxetine has been introduced in the EMLc for antidepressant disorders in children above 8 years of age.
Uncertainty: yes.

Cost
Amitriptyline is widely available and inexpensive.
Uncertainty: none.

Research agenda
Trials in children concerning the safety and the efficacy of tricyclic antidepressants and selective SSRIs and newer antidepressants of the class of serotonin and norepinephrine reuptake inhibitors for neuropathic pain are needed.

A2.2.12 Adjuvants in neuropathic pain: anticonvulsants

Clinical question
In children with persisting neuropathic pain, what is the evidence for the use of gabapentin as compared to carbamazepine in order to achieve rapid, effective and safe pain control?

Recommendation
At present, it is not possible to make recommendations for any anticonvulsant as an adjuvant in the management of neuropathic pain in children.

Domains and considerations

Quality of evidence
No systematic reviews and/or RCTs in children were identified. There is no evidence for the use of anticonvulsants for the management of neuropathic pain in children. The use of gabapentin has been promoted for neuropathic pain in children and there is increasing clinical experience for its use in the paediatric population. However, no comparative study with carbamazepine and no study to determine the adjuvant potential of gabapentin in the treatment of persisting neuropathic pain in children could be retrieved. Not all adult trial data have been published in their entirety and, therefore, evaluation for gabapentin's efficacy in reducing neuropathic pain in adults has yet to be systematically reviewed (*87*).
Uncertainty: yes.

Risks/benefits
Benefits
There is extensive experience with carbamazepine as an anticonvulsant in adults and children. Gabapentin is registered for use as anticonvulsant in children above the age of 3 years.
Risks
Carbamazepine has increased risks and clinical monitoring requirements as compared with newer anticonvulsants.
Uncertainty: yes.

Cost
Carbamazepine is widely available and inexpensive, but there may be additional costs associated with monitoring. The high cost of gabapentin may limit availability.
Uncertainty: none.

Research agenda
Trials and comparative studies on the safety and efficacy of gabapentin and carbamazepine in children with persisting pain are needed.

A2.2.13 Adjuvants in neuropathic pain: ketamine

Clinical question
In children with persisting neuropathic pain, what is the evidence for the use of ketamine as compared to placebo in order to achieve rapid, effective and safe pain control?

Recommendation
At present, it is not possible to make recommendations regarding the benefits and risks of ketamine as an adjuvant to opioids for neuropathic pain in children.

Domains and considerations

Quality of evidence
There is limited evidence for ketamine in sub-anaesthetic (low) dose as an adjuvant to strong opioids in palliative care in adults (*88*). There are no studies in children investigating the use of ketamine as an adjuvant to opioid for refractory neuropathic pain.
Uncertainty: yes.

Values and acceptability
In favour
Ketamine in sub-anaesthetic (low) dose may be considered as an adjuvant to opioid for refractory neuropathic pain.
Against
Unknown
Uncertainty: yes.

Research agenda
Trials concerning the efficacy and safety of sub-anaesthetic (low) dose ketamine as an adjuvant to opioid in children with refractory neuropathic pain are needed.

A2.2.14 Adjuvants in neuropathic pain: local anaesthetics

Clinical question
In children with persisting neuropathic pain, what is the evidence for the systemic use of local anaesthetics as compared to placebo in order to achieve rapid, effective and safe pain control?

Recommendations
At present, it is not possible to make recommendations regarding the benefits and risks of the systemic use of local anaesthetics for persisting neuropathic pain in children.

Domains and considerations

Quality of evidence
No evidence was retrieved for the use of systemic local anaesthetics as adjuvants for pain relief in children. There is evidence in adults that intravenous lidocaine and its oral analog mexiletine are more effective than a placebo in decreasing neuropathic pain and can relieve pain in selected patients (*89*).
Uncertainty: yes.

Research agenda
Trials concerning the efficacy and safety of the systemic use of local anaesthetics as adjuvants in persisting neuropathic pain in children are needed.

A2.2.15 Adjuvants for pain during muscle spasm or spasticity: benzodiazepines and baclofen

Clinical question
In children with persisting pain due to medical illnesses, should benzodiazepines as compared to baclofen be used as adjuvant medicines in order to achieve and maintain effective and safe pain control during muscle spasm and spasticity?

Recommendation
At present, it is not possible to make a recommendation for the use of benzodiazepines and/or baclofen as an adjuvant in the management of pain in children with muscle spasm and spasticity.

Domains and considerations

Quality of evidence
A World Health Organization summary of evidence in palliative care identified that there was no good evidence base for the use of these agents in that setting for pain associated with muscle spasm (*72*). However, the panel noted that this is routine practice. There is no good evidence base for the use of baclofen and benzodiazepines in the setting of pain associated with spasticity in adults (*90, 91*). No studies have been retrieved in children.
Uncertainty: yes.

Risks/benefits
Benefits
Unknown, although both baclofen and benzodiazepines have long been used in the management of muscle spasm and spasticity.
Risks
The adverse effects associated with these medicines are well described.
Uncertainty: yes.

Research agenda
Trials concerning the efficacy and safety of baclofen and benzodiazepines as adjuvants in the management of muscle spasm and spasticity in children are needed.

A2.3 Non-pharmacological interventions

Only one systematic review was identified on non-pharmacological interventions (Annex 4. *Evidence retrieval and appraisal*, GRADE Table 16). The one systematic review considered types of pain falling both within and outside the scope of these guidelines. It was felt by the WHO Guidelines Development Group that the scope had to be enlarged to comprise a wider spectrum of non-pharmacological interventions beyond physical exercise, physiotherapy and cognitive behavioural therapy; and that adequate expertise was needed to assess the evidence and formulate recommendations.

ANNEX 3. BACKGROUND TO THE HEALTH SYSTEM RECOMMENDATIONS

This annex reports the detailed considerations by the WHO Guidelines Development Group for each recommendation as mentioned in Chapter 4. *Improving access to pain relief in health systems.* They were formulated at a meeting held at the Rockefeller Conference Center in Bellagio, Italy, in March 2010. These recommendations arise from an appraisal of the evidence retrieved and reported in Annex 4. *Evidence retrieval and appraisal,* considerations and recommendations from the WHO policy guidelines *Ensuring balance in national policies on controlled substances: availability and accessibility of controlled medicines* (*95*) and additional evidence and values.

Health systems question

What is the evidence for the use of task shifting from medical doctors to other health professionals in prescribing, titrating and monitoring opioid analgesics to ensure rapid, effective and safe pain control?

Recommendations

20. Education of health professionals in the standardized management of persisting pain in children with medical illnesses and in the handling of the necessary medicines, including opioid analgesics, is encouraged.
21. Health professionals will be allowed to handle opioids within their scope of practice or professional role based on their general professional licence without any additional licensing requirements.
22. In addition, countries may consider, subject to their situation, allowing other professions to diagnose, prescribe, administer and/or dispense opioids for reasons of flexibility, efficiency, increased coverage of services and/or improved quality of care.
23. The conditions under which such permission is granted should be based on the demonstration of competence, sufficient training, and personal accountability for professional performance.

Guidelines Development Group experts' opinion

Domains and considerations

Evidence

Reference is made to the *Cochrane Systematic Review* on substitution of doctors by nurses in primary health care (*118*); to the bibliography reported on the 2008 WHO guidelines on task shifting (*111*); and to the tables on health system interventions, and opioid analgesics prescription and pain services in Uganda and the United Kingdom, and in the Indian State of Kerala and the Malaysian State of Sarawak. (See Annex 4.2, *Studies retrieved on health system recommendations.)*

Guideline 11 of the WHO policy guidelines for *Ensuring balance in national policies on controlled substances* also supports the recommendation that no health professional should require additional licensing to handle opioids: "Appropriately trained and qualified physicians, and, if applicable, nurses and other health professionals, at all levels of health care should be allowed to prescribe and administer controlled medicines, based on their general professional licence, current medical knowledge and good practice without further licence requirements." (*95*)

Values
The panel places high value on management of pain.

Research
More documentation is desired which considers both qualitative and quantitative data on health-system interventions around the delegation of tasks from medical doctors to other health professionals to ensure service coverage for pain relief in national health systems.

ANNEX 4. EVIDENCE RETRIEVAL AND APPRAISAL

This Annex 4 provides information on the evidence for the clinical recommendations, the studies retrieved on health system recommendations and the studies retrieved in the third step of the evidence retrieval process.

A4.1 GRADE profiles

The following evidence profiles were produced by applying the GRADE Working Group approach to determine the quality of evidence for the questions addressed. They refer to the first and second steps of the evidence retrieval process, as reported in Annex 2, Section 2.1 *Development process*.

GRADE Table 1A

Author: Wiffen PJ
Date: 16-04-2009
Question: Should paracetamol vs. ibuprofen be used in children with musculoskeletal trauma (acute pain)? Mean age: approximately 12 years.
Setting: Emergency department, Ottawa, ON, Canada.
Bibliography: Clark E et al. A randomised controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. *Paediatrics*, 2007, 119:460–467.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Ibuprofen	Relative (95% CI)	Absolute	Quality
Pain relief measured as reduction in VAS at 60 minutes (follow-up: 120 minutes; measured with: VAS pain; range of scores: 0–100; better indicated by lower values)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	One single dose study	112 (ITT)	112 (ITT)	–	Paracetamol mean 12 lower (16 to 8 lower) Ibuprofen 24 lower (29 to 20 lower)	LOW
Minor adverse events (AEs) (e.g. nausea, sleepiness, constipation)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	Gastrointestinal bleeding is not reported	–	–	–	8/104 Paracetamol 11/101 Ibuprofen	LOW

CI, confidence interval; VAS, visual analogue scale; ITT, intention to treat.

[a] Study in acute pain setting. Doses: paracetamol 15mg/kg (max 650 mg), ibuprofen 10 mg/kg (max 600 mg). Data extracted as reported.

[b] Acute pain study. No significant difference between groups for adverse effects.

GRADE Table 1B

Author: Wiffen PJ
Date: 16-04-2009
Question: Should ibuprofen vs. codeine be used in children with musculoskeletal trauma (acute pain)? Mean age: approximately 12 years.
Setting: Emergency department, Ottawa, ON, Canada.
Bibliography: Clark E et al. A randomised controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. *Paediatrics*, 2007, 119:460–467.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Codeine	Relative (95% CI)	Absolute	Quality
Pain relief measured as reduction in VAS at 60 minutes (follow-up: 120 minutes; measured with: VAS pain; range of scores: 0–100; better indicated by lower values)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	112 (ITT)	112 (ITT)	–	Paracetamol mean 12 lower (16 to 8 lower) Codeine 11 mean lower (16 to 5 lower)	LOW
Minor adverse events (such as nausea, sleepiness, constipation)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	The variability in bio-transformation of codeine not considered	–	–	–	8/104 Paracetamol 8/104 Codeine	LOW

CI, confidence interval; VAS, visual analogue scale; ITT, intention to treat.

[a] Study in acute pain setting. Doses: paracetamol 15 mg/kg (maximum 650 mg), codeine 1 mg/kg (maximum 60 mg). Data extracted as reported.

[b] Acute pain study. No significant difference between groups for adverse effects.

GRADE Table 2

Author: Wiffen PJ
Date: 02-12-2008
Question: Should IV morphine PCA vs. IV hydromorphone PCA be used for mucositis pain in children aged approximately 14 years?
Settings: Children's hospital, Boston, MA, USA.
Bibliography: Collins J et al. Patient controlled analgesia for mucositis pain in children. A three period crossover study comparing morphine and hydromorphone. *Journal of Pediatrics*, 1996, 129:722–728.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV morphine PCA	IV hydromorphone PCA	Relative (95% CI)	Absolute	Quality
Efficacy (follow-up: 10–33 days; mean daily pain scores)[a]											
1	Randomized trial	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	10/10 (100%)	10/10 (100%)	No difference	Not pooled Not pooled	LOW
Adverse events (follow-up: mean 10 days; patient self report)											
1	Randomized trial	Serious[b]	No serious inconsistency	Serious[b]	No serious imprecision	None	No data	No data	No statistical difference	–	LOW

IV, intravenous; PCA, patient-controlled analgesia; CI, confidence interval.

[a] No statistical difference between mean daily pain scores. Dose potency hydromorphone to morphine estimated at 5.1:1 (usually considered as 7:1).

[b] Only 10 participants – crossover study. Data extracted as reported.

[c] Assessed mucositosis pain not cancer pain.

GRADE Table 3

Author: Wiffen PJ
Date: 08-12-2008
Question: Should intranasal fentanyl vs. intravenous morphine be used in acute pain of bone fractures in children aged 7–15 years?
Settings: Children's Hospital, Australia.
Bibliography: Borland M et al. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Annals of Emergency Medicine*, 2007, 49:335–340.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intranasal fentanyl	IV morphine	Relative (95% CI)	Absolute	Quality
VAS pain intensity score (follow-up: mean 30 minutes; measured with: VAS score; range of scores: 1–100; better indicated by lower values)[a]											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious -2[b]	No serious imprecision	None	33	34	–	Mean difference between the two groups -4 (-16 to 8)[c]	LOW
Adverse events (follow-up: mean 30 minutes; physician or nurse report[c])											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious -2[b]	No serious imprecision	None	See below[d]	See below[d]	No evaluable data	–	LOW

IV, intravenous; CI, confidence interval; VAS, visual analogue scale.

[a] Intervention is intranasal fentanyl 1.4 mg/kg. Control is IV morphine approx 0.1 mg/kg.

[b] Acute pain study not cancer pain.

[c] Both groups achieved greater than 30 mm reduction in pain VAS score.

[d] Three out of 33 children had a bad taste in mouth after nasal spray, and one vomited on fentanyl. One had a flush at injection site after IV morphine. No other adverse events.

GRADE Table 4

Author: Wiffen PJ
Date: 16-04-2009
Question: Should oral transmucosal fentanyl citrate vs. intravenous morphine be used for extremity injury or suspected fracture in children aged 8–18 years?
Setting: Pediatric tertiary care emergency department. Denver, CO, USA.
Bibliography: Mahar P et al. A randomised clinical trial of oral transmucosal fentanyl citrate vs intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatric Emergency Care*, 2007, 23:544–548.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oral transmucosal fentanyl	IV morphine	Relative (95% CI)	Absolute	Quality
Reduction in VAS pain intensity (follow-up: 75 minutes)[a]											
1	Randomized trial	Serious[c]	No serious inconsistency	Serious[d]	No serious imprecision	None	50 ITT	45 ITT	Not calculated[b]	–	LOW
Adverse events (follow-up mean 75 minutes)											
1	Randomized trial	Serious[c]	No serious inconsistency	Serious[d]	No serious imprecision	None	8 adverse events	2 adverse events	–	–	LOW

IV, intravenous; CI, confidence interval; ITT, intention to treat.

[a] Intervention is transmucosal fentanyl 10–15 mcg/kg; control is IV morphine 0.1mg/kg.

[b] Reduction in VAS pain intensity greater than 40 mm in morphine IV group and greater than 60 mm in oral transmucosal fentanyl.

[c] Open study, not blinded.

[d] Study in acute pain not cancer pain.

GRADE Table 5 (table excluded during evidence appraisal as not addressing the clinical questions on comparison of strong opioids and route of administration within the scope of these guidelines)

Author: Wiffen PJ
Date: 17-04-2009
Question: Should epidural morphine vs. epidural fentanyl or epidural hydromorphone be used for post-operative pain control for orthopaedic surgery in children aged 3–19 years?
Settings: Children's hospital, Los Angeles, CA, USA.
Bibliography: Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for post-operative pain control in children undergoing orthopaedic surgery. *Paediatric Anesthesia*, 1999, 9:419–422.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Epidural morphine	Epidural fentanyl / Epidural hydromorphone	Relative (95% CI)	Absolute	Quality
Post-operative pain scores (follow-up: mean 30 hours; 5-point VAS scale)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	Epidural route	30	30 30	Descriptive data only. Good pain relief achieved, similar in all groups[b,c]	–	VERY LOW
Adverse events (follow-up: mean 30 hours)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	Epidural route	–	–	Descriptive data only[d]	–	VERY LOW

CI, confidence interval; VAS, visual analogue scale.

[a] Acute post-operative pain: morphine 10 mcg/kg/h; hydromorphone 1 mcg/kg/h; fentanyl 1 mcg/kg/h.

[b] Ninety participants: 30 per group.

[c] All groups reported good to excellent pain relief. No statistically significant difference.

[d] Respiratory depression, somnolence, nausea, vomiting, pruritis and urinary retention, all at greater incidence in morphine group.

GRADE Table 6

Author: Wiffen PJ
Date: 17-04-2009
Question: Should morphine vs. buprenorphine be used for post-operative pain after orthopaedic surgery in children aged 6 months to 14 years?
Settings: Children's hospital, Helsinki, Finland.
Bibliography: 1. Maunuksela E-l et al. Double-blind multiple-dose comparison of buprenorphine and morphine in postoperative pain of children. *British Journal of Anaesthesia*, 1988, 60:48–55; 2. Maunuksela E-l et al. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesthesia Analgesia*, 1988, 67:233–239.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV morphine	IV buprenorphine	Relative (95% CI)	Absolute	Quality
Pain intensity (follow-up: 1–3 days[a]; 10-point CATPI by nurses; verbal rating by patient)											
2	Randomized trials	No serious limitations	No serious inconsistency	Serious -2[b]	No serious imprecision	None	Study 1 (28) Study 2A (32)	Study 1 (29) Study 2A (28)	Descriptive data, both classed as good or very good[c]	–	LOW
Adverse events (follow-up: 1–3 days[a]; not clear apart from categorical scale for sedation)											
2	Randomized trials	No serious limitations	No serious inconsistency	Serious -2[b]	No serious imprecision	None	Descriptive data only[d]	–	No evaluable data	–	LOW

IV, intravenous; CI, confidence interval; CATPI, categorical pain intensity.

[a] Study 1: 24 hours; Study 2: to the morning of the 3rd post-operative day.

[b] Acute post-operative pain study.

[c] Morphine and buprenorphine as analgesics assessed as good or very good in both studies.

[d] Study 1 (morphine 100 or 50 mcg/kg or buprenorphine 3 or 1.5 mcg/kg) both drugs produced marked sedation – no difference between the groups. Study 2A (morphine 100 mcg/kg or buprenorphine 3 mcg/kg). Study 2A and 2B: 13 reports of adverse events in 28 participants on buprenorphine, 19 reports of AEs in 32 participants on morphine. Vomiting: eight reports in participants on buprenorphine, five reports in participants on morphine. Urinary retention: six reports in each group.

Bibliography: Study 2B: Maunuksela E-l et al. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesthesia Analgesia*, 1988, 67:233–239.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IM morphine[a]	Sublingual buprenorphine[a]	Relative (95% CI)	Absolute	Quality
Pain relief (5 point CATPI by patient)[b]											
2	Rand-omized trials	No serious limita-tions	No serious incon-sistency	Serious[c]	No serious impreci-sion	None	Study 2B (32)	Study 2B (28)	–	Morphine 11/32 stated analgesia poor or just satisfactory Buprenor-phine 10/28 stated analgesia poor or just satisfactory	LOW

CI, confidence interval; CATPI, categorical pain intensity.

[a] Study 2B: IM morphine 150 mcg/kg or sublingual buprenorphine 5–7.1 mcg/kg; both no more than 6 doses in 24 hours.

[b] Study 2B is a continuation of Study 2A in a surgical ward for days 2–4 post-operative.

[c] Acute post-operative pain study.

GRADE Table 7

Author: Wiffen PJ
Date: 17-04-2009
Question: Should morphine PCA vs. ketobemidone PCA be used for post-operative pain in children aged 6–16?
Setting: Children's hospital, Stockholm, Sweden.
Bibliography: Jylli L et al. Comparison of the analgesic efficacy of ketobemidone and morphine for the management of postoperative pain in children: a randomized controlled study. *Acta Anaesthesiologica Scandinavica*, 2002, 48:1256–1259.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine PCA	Ketobemidone PCA	Relative (95% CI)	Absolute	Quality
Pain intensity VAS (follow-up: 3–73 hours)											
1	Rand-omized trial	No serious limita-tions	No serious incon-sistency	Serious -2[a]	No serious impreci-sion	None	30	27	No significant difference between groups[b,c]	–	LOW
Adverse events (follow-up 3–73 hours; different scales, not stated who assessed)											
1	Rand-omized trial	No serious limita-tions	No serious incon-sistency	Serious -2[a]	No serious impreci-sion	None	See below[b,d]	–	–	–	LOW

PAC, patient-controlled analgesia; CI, confidence interval; VAS, visual analogue scale.

[a] Acute post-operative pain study.

[b] Morphine PCA: total consumption 17.4 mcg/kg/h; ketobemidone PCA total consumption 16.4 mcg/kg/h.

[c] Both groups achieved reduction in pain VAS scores of > 30 mm each day. No significant difference between the groups.

[d] Both groups experienced nausea, vomiting, itching and over-sedation. No significant difference between the groups.

GRADE Table 8 (table excluded during evidence appraisal as undifferentiated abdominal pain was not included in the scope of these guidelines)

Author: Wiffen PJ
Date: 07-01-2009
Question: Should oxycodone (buccal) vs. placebo be used for undifferentiated abdominal pain in children aged 4–15 years?
Setting: Teaching Hospital, Finland.
Bibliography: Kokki et al. Oxycodone vs. placebo for undifferentiated abdominal pain. *Archives of Pediatrics & Adolescent Medicine*, 2005, 159:320–325.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oxycodone buccal)	Placebo	Relative (95% CI)	Absolute	Quality
Sum of pain intensity difference (follow-up: mean 3.5 hours; better indicated by higher values)											
1	Rand-omized trial	No serious limita-tions	No serious incon-sistency	Serious[a]	No serious impreci-sion	None	32	31	–	MD 13 higher (2–24 higher)[b]	MOD-ERATE
Adverse events (follow-up mean 3.5 hours; not stated)											
1	Rand-omized trial	No serious limita-tions	No serious incon-sistency	Serious[a]	No serious impreci-sion	None	–	– –	Descrip-tive data only[c]	– –	MOD-ERATE

CI, confidence interval; MD, mean difference.

[a] Study of abdominal pain not persisting pain.

[b] Oxycodone performed better than placebo.

[c] One patient developed headache and another urticaria on oxycodone. No sedation, hypoxia or hypotension observed.

GRADE Table 9 (table excluded during the evidence appraisal as not addressing the clinical questions on comparison of strong opioids and route of administration within the scope of these guidelines)

Author: Wiffen PJ
Date: 17-04-2009
Question: Should oxycodone vs. ibuprofen or oxycodone/ibuprofen combination be used for initial management of orthopaedic injury related pain in children aged 6–18 years?
Setting: Paediatric emergency department, USA.
Bibliography: Koller D et al. Effectiveness of oxycodone, ibuprofen or the combination in the initial management of orthopaedic injury related pain in children. *Emergency Care*, 2007, 23:627–633.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oxycodone	Ibuprofen / Oxycodone-ibuprofen combination	Relative (95% CI)	Absolute	Quality
Pain (follow-up: mean 120 minutes; Faces Pain Scale, VAS reported by parents and nurses)[a]											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious -2[b]	No serious imprecision	None	22	22 22	No significant difference between the three treatment groups[c]	– –	LOW
Adverse events (follow-up: mean 120 minutes)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious -2[a]	No serious imprecision	None	Descriptive data[d]	– –	–	– –	LOW

CI, confidence interval; VAS, visual analogue scale.

[a] Doses: oxycodone 0.1 mg/kg (maximum 10 mg), ibuprofen 10 mg/kg (maximum 800 mg), combination both at trial doses.

[b] Acute pain – orthopaedic injuries.

[c] Good pain relief achieved in the three groups. Reduction in Faces Pain Scales from approximately 7 to approximately 3 (Scale 0–10).

[d] Eleven participants reported 14 adverse events, 9 of these in the combination group. Drowsiness was the most common but numbers were low: ibuprofen 3, combination 3, oxycodone 1.

GRADE Table 10

Author: Wiffen PJ
Date: 17-04-2009
Question: Should oral morphine be used for cancer pain in children?
Settings: 18 countries.
Bibliography: Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews*, 2007 (4):CD003868.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate-release morphine	Modified- release morphine	Relative (95% CI)	Absolute	Quality
Pain relief (follow-up: 4–30 days; validated scales)											
15	Randomized trials	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	Not calculated	Not calculated	Similar results from both arms[b]	–	MODERATE
Adverse events (follow-up: 3–30 days; generally self report)											
15	Randomized trials	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	Data not available by group[c]	–	No evaluable data[c]	–	MODERATE

CI, confidence interval.

[a] All studies conducted in adults: setting 18 countries (11 European, 3 Asia, 2 North America, 2 Oceania).

[b] Studies showed that similar analgesia could be obtained using either modified-release or immediate-release morphine. Total patients: 3615 (54 RCTs).

[c] No data available by group. Approximately 6% of participants (adults) in the studies who received morphine (any type) found the adverse effects intolerable.

GRADE Table 11

Author: Wiffen PJ
Date: 02-12-2008
Question: Should PCA morphine vs. IM morphine be used in post-operative pain in children and adolescents with a mean age of 13 years?
Settings: Children's hospital, Boston, MA, USA.
Bibliography: Berde C et al. Patient controlled analgesia in children and adolescents: a randomized prospective comparison with intramuscular administration of morphine for postoperative analgesia. *Journal of Pediatrics*, 1991, 118:460–466.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCA morphine	IM morphine	Relative (95% CI)	Absolute	Quality
Patient pain scores (follow-up: 48 hours; achieved a VAS pain scale of at least mild pain)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	10/32 (31.3%)[b]	5/23 (21.7%)	Not statistically significant NNT 10 (-7 to 3)	–	MODERATE
Adverse events (follow-up: mean 48 hours; patient self report and nurse observation)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	Descriptive data only[c]	Descriptive data only[c]	–	–	MODERATE

PCA, patient-controlled analgesia; IM, intramuscular; CI, confidence interval; VAS, visual analogue scale; NNT, number needed to treat.

[a] Study of post-operative orthopaedic pain.

[b] Only PCA vs. IM data used. A third group included a baseline continuous infusion of morphine. Data excluded for PCA plus as background infusion. Data extracted as reported.

[c] No respiratory depression in either groups. Sedation was less on PCA than on IM. No difference between the two groups in nausea or return to gastrointestinal function. No difference between the two groups in urinary retention.

GRADE Table 12

Author: Wiffen PJ
Date: 15-02-2010
Question: Should PCA morphine with background infusion vs. continuous morphine infusion be used for post-operative pain in children?
Setting: Not stated.
Bibliography: Peters JWB et al. Patient controlled analgesia in children and adolescents: a randomised controlled trial. *Paediatric Anaesthesia*, 1999, 9:235–241.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PCA morphine with background infusion[a]	Continuous orphine infusion[a]	Relative (95% CI)	Absolute	Quality
Mild pain at 2 days (follow-up: mean 2 days; daily mean pain scores (VASPI)											
1	Rand-omized trial	Serious[b]	No serious incon-sistency	Serious[c]	No serious impre-cision	None	7/24 (29.2%)[d]	15/23 (65.2%)[d]	–	–	LOW

PCA, patient-controlled analgesia; CI, confidence interval; VASPI, visual analogue scale of pain intensity.

[a] Results are the number of patients who achieved "mild" pain on day 2. Results calculated from article's Figure 1.

[b] No details of randomization or allocation concealment provided.

[c] Post-operative pain model not chronic pain.

[d] Doses: PCA morphine bolus of 15 mcg/kg lockout of 10 minutes and background of 15 mcg/kg/hr; continuous morphine 20–40 mcg/kg/hr.

GRADE Table 13

Author: Wiffen PJ
Date: 17-04-2009
Question: Should oral morphine vs. continuous intravenous morphine be used for painful episodes of sickle cell disease in children aged 5–17 years?
Settings: Jacobson study: Children's hospital, Toronto, ON, Canada.
Bibliography: 1. Dunlop R, Bennett KCLB. Pain management for sickle cell disease in children and adults. *Cochrane Database of Systematic Reviews*, 2006, (2):CD003350; 2. Jacobson et al. Randomised trial of oral morphine for painful episodes of sickle-cell crisis in children. *Lancet*, 1997, 350:1358–1361.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Modified- release morphine	Continuous IV morphine	Relative (95% CI)	Absolute	Quality
Pain relief based on Oucher scale (measured with: Oucher scale; range of scores: 0–100; better indicated by lower values)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	27[b]	29[c]	–	No significant difference	MODERATE
Adverse events (non-directed questionnaire used daily)											
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	Descriptive data only[d]	–	–	–	MODERATE

IV, intravenous; CI, confidence interval.

[a] Study is for sickle cell crisis – only oral morphine RCT found for acute or cancer pain. Data extracted as reported.

[b] Oral morphine 1.9 mg/kg every 12 hours.

[c] Intravenous morphine 0.04 mg/kg every hour.

[d] Oral morphine group (27 participants) recorded 62 adverse events, 16 "severe intensity events". Intravenous morphine group (29 participants) recorded 52 adverse events, 19 "severe intensity events". The definition of "severe intensity" reports is not provided.

GRADE Table 14

Author(s): Wiffen PJ
Date: 08-12-2008
Question: Should nebulized fentanyl vs. intravenous fentanyl be used for acute pain requiring IV analgesics in patients aged 6 months–17 years?
Setting: Children presenting at an emergency department, Minnesota, USA.
Bibliography: Miner JR et al. Randomized clinical trial of nebulized fentanyl citrate vs. IV fentanyl citrate in children presenting to the emergency department with acute pain. *Academic Emergency Medicine*, 2007, 14:895–898.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Nebulized fentanyl	IV fentanyl	Relative (95% CI)	Absolute	Quality
Reduction in VAS pain intensity score (follow-up: mean 30 minutes; better indicated by lower values)											
1	Randomized trial	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	27[c]	14	–	Not calculated Only 11/41 assessed[d]	VERY LOW
Adverse events (not stated[d])											
1	Randomized trial	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	–	–	–	No adverse events[e]	LOW

IV, intravenous; CI, control interval; VAS, visual analogue scale.

[a] Open study. Some patients randomized to IV were given inhaled fentanyl due to parent preference. Pain was assessed by physician in patients aged 6 years and below (30 patients), and by patients above 6 years (11 patients).

[b] Acute pain not cancer pain.

[c] Intervention is nebulized fentanyl 3 mcg/kg; control is IV fentanyl 1.5 mcg/kg.

[d] Both groups appear to have achieved a significant reduction in pain VAS score according to treating physician.

[e] States "no adverse events occurred in either group".

GRADE Table 15

Author: Wiffen PJ
Date: 26-05-2009
Question: Should transdermal fentanyl be used for cancer pain in children?
Setting: Not stated.
Bibliography: Zernikow B, Michel E, Anderson B. Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *The Journal of Pain*, 2007, 8:187–207.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Transdermal fentanyl	Control	Relative (95% CI)	Absolute	Quality
Satisfaction with therapy (patient or professional judgement)											
11	Observational studies	Very serious[a]	Serious[b]	Serious[c]	No serious imprecision	Reporting bias[d]	311	Not reported	Not pooled	Not pooled	LOW

CI, confidence interval.

[a] All observational studies: 6 studies were of 10 patients or less; 1 study was of 199 patients.

[b] Different conditions, different doses, some acute, and different populations.

[c] Not all cancer pain, some post-operative pain.

[d] Observational studies are difficult to identify by current search techniques.

GRADE Table 16

Author: Wiffen PJ
Date: 27-04-2009
Question: Should cognitive behaviour therapy (CBT) or relaxation be used for the management of chronic and recurrent non-headache pain in children and adolescents?
Setting: Not stated.
Bibliography: Eccleston C et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database of Systematic Reviews*, 2009, (2):CD003968.

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CBT alone or in combination with other non-pharmacological interventions	Control (standard medical care)	Relative (95% CI)	Absolute	Quality
Pain (follow-up 1.5–12 months; measured with: pain scores – variety; range of scores; better indicated by less)											
5	Rand-omized trials	No serious limita-tions	No serious incon-sist-ency	Seri-ous[a]	No serious impre-cision	None	143	95	–	SMD[b] -0.94 (-1.43 to -0.44)	MOD-ERATE

CBT, cognitive behaviour therapy; CI, confidence interval; SMD, standardized mean difference.

[a] Participants had a variety of pain including fibromyalgia and recurrent abdominal pain. One study (Hicks 2006) was with mixed headache and abdominal. No studies included malignant pain. Data extracted as reported.

[b] Standardized mean difference as calculated in the review.

A4.2 Studies retrieved on health system recommendations

Opioid analgesics prescription

Country	**Uganda**
Health professional	Palliative-care nurses and clinical officers.
Intervention	• Morphine prescription upon specialized training: - Clinical Palliative Care Course (9 months: 8 weeks – theory, 12 weeks – hospice, 10 weeks – HIV/palliative care, 10 weeks in their own place of work). • Amendment of national legislation to enable nurses and clinical officers to prescribe opioid medicines as part of their clinical practice (professional licence).
Setting	Hospices/palliative-care teams in hospitals/health districts.
Bibliography	• Clark D et al. Hospice and palliative care development in Africa: a multi-method review of services and experiences. *Journal of Pain and Symptom Management,* 2007, 33:698–710. • Jagwe J, Merriman A. Uganda: delivering analgesia in rural Africa – opioid availability and nurse prescribing. *Journal of Pain and Symptom Management,* 2007, 33:547–551. • Logie DE, Harding R. An evaluation of a morphine public health programme for cancer and AIDS pain relief in Sub-saharan Africa. *BMC Public Health,* 2005, 5:82.

Country	**United Kingdom**
Health professional	Nurses, pharmacists.
Intervention	Emergency prescription of opioid analgesics for cancer pain (when the physician is not able to physically provide a prescription) as part of the two systems below: • training and certification to allow nurses to prescribe any medicine that has been included in the Clinical Management Plan made by a medical doctor (Nurse Supplementary Prescribers = NSPs); • training and certification to allow nurses to assess, diagnose and prescribe independently (Nurse Independent Prescribers = NIPs).
Setting	National health system.
Bibliography	• Cherny NI et al. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Annals of Oncology*, 2010, 21:615–626. • Stenner K, Courtenay M. Benefits of nurse prescribing for patients in pain: nurses' views. *Journal of Advanced Nursing*, 2008, 63:27–35.

Country	**Lithuania**
Health professional	Nurses, pharmacists.
Intervention	Emergency prescription of opioids for cancer pain (when the physician is not able to physically provide a prescription).
Setting	National health system
Bibliography	• Cherny NI et al. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Annals of Oncology*, 2010, 21:615–626. Note: this article just refers to this intervention, but does not provide any description of the system established for emergency prescriptions in the country.

Pain relief services and opioid analgesics supply

Country	**State of Sarawak, Malaysia**
Health professional	Nurses, pharmacists, community health workers, volunteers.
Intervention	Home-based palliative care and medicine supply. The opioid analgesic prescription is made by an oncologist, but nurses play an important role in medicine supply for the home-based palliative-care programme.
Setting	Home-based palliative care, high turnover of medical doctors in the health districts.
Bibliography	• Devi BCR, Tang TS, Corbe M. Setting up home-based palliative care in countries with limited resources: a model from Sarawak, Malaysia. *Annals of Oncology*, 2008, 19:2061–2066.
Country	**State of Kerala, India**
Health professional	Nurses.
Intervention	• Medicine supply (stock and dispensing) from pharmacists to nurses. • State exception on the requirement of a pharmacist for medicines dispensing service.
Setting	State palliative-care programme
Bibliography	• Rajagopal MR, Joranson DE, Gilson AM. Medical use, misuse, and diversion of opioids in India. *Lancet*, 2001, 358:139–143. Note: the full description of why a nurse instead of a pharmacist is needed is not provided in the article (e.g. number of available pharmacists in the State and their distribution in urban and rural areas for the medicines dispensing service).

A4.3 Studies retrieved in the third step of the evidence retrieval process

This list refers to the third step of evidence retrieval process as reported in Annex 2, Section A2.1 *Development process*. Listed items were retrieved while sourcing observational studies for interventions where no systematic reviews and no randomized control trials were obtained in the first two rounds of evidence retrieval.

For this third round of evidence retrieval, the request was forwarded to the Expanded Review Panel for the WHO pain guidelines and also to the WHO Expert Panel on Drug Evaluation. The articles retrieved include observational studies, pharmacokinetics and pharmacodynamics studies and also a few additional randomized controlled studies in children.

Analgesics

Anderson BJ, Palmer GM. Recent pharmacological advances in paediatric analgesics. *Biomedicine & Pharmacotherapy*, 2006, 60:303–309.

Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *New England Journal of Medicine*, 2002, 347:1542.

Olkkola KT, Hamunen K, Maunuksela EL. Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clinical Pharmacokinetics*, 1995, 28:385–404.

Schiessl C et al. Use of patient-controlled analgesia for pain control in dying children. *Supportive Care in Cancer*, 2008, 16:531–536.

Zernikow B et al. Paediatric cancer pain management using the WHO analgesic ladder – results of a prospective analysis from 2265 treatment days during a quality improvement study. *European Journal of Pain*, 2006, 10:587–595.

Paracetamol

Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *European Journal of Clinical Pharmacology*, 2001, 57:559–569.

Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *British Journal of Clinical Pharmacology*, 2000, 50:125–134.

Anderson BJ et al. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology*, 2002, 96:1336–1345.

Anderson BJ et al. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *British Journal of Clinical Pharmacology*, 1998, 46:237–243.

Van der Marel CD et al. Paracetamol and metabolite pharmacokinetics in infants. *European Journal of Clinical Pharmacology*, 2003, 59:243–251.

Van der Marel CD et al. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. *Clinical Pharmacology & Therapeutics*, 2001, 70:82–90.

IV paracetamol

Allegaert K et al. Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 2004, 89:F25–F28.

Allegaert K et al. Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. *European Journal of Clinical Pharmacology*, 2004, 60:191–197.

Anderson BJ et al. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Paediatric Anaesthesia*, 2005, 15:282–292.

Kumpulainen E et al. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics*, 2007, 119:766–771.

Rectal paracetamol

Anderson BJ, Woolard GA, Holford NH. Pharmacokinetics of rectal paracetamol after major surgery in children. *Paediatric Anaesthesia*, 1995, 5:237–242.

Hahn TW et al. Pharmacokinetics of rectal paracetamol after repeated dosing in children. *British Journal of Anaesthesia*, 2000, 85:512–519.

Howell TK, Patel D. Plasma paracetamol concentrations after different doses of rectal paracetamol in older children: a comparison of 1 g vs. 40 mg.kg-1. *Anaesthesia*, 2003, 58:69–73.

Montgomery CJ et al. Plasma concentrations after high-dose (45 mg.kg-1) rectal acetaminophen in children. *Canadian Journal of Anesthesia*, 1995, 42:982–986.

Paracetamol versus Ibuprofen

Bertin L et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *Journal of Pediatrics*, 1991, 119:811–814.

Kelley MT et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. Clinical Pharmacology & Therapeutics, 1992, 52:181–189.

Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *Journal of the American Medical Association*, 1995, 273:929–933.

Perrott DA et al. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. *Archives of Pediatrics & Adolescent Medicine*, 2004, 158:521–526.

Tramadol

Allegaert K et al. Tramadol disposition in the very young: an attempt to assess in vivo cytochrome P-450 2D6 activity. *British Journal of Anaesthesia*, 2005, 95:231–239.

Bozkurt P. Review article: use of tramadol in children. *Pediatric Anesthesia*, 2005, 15:1041–1047 doi:10.1111

Brown, SC, Stinson J. Treatment of pediatric chronic pain with tramadol hydrochloride: siblings with Ehlers-Danlos syndrome – Hypermobility type (case report). *Pain Research & Management*, 2004, 9:209–211.

Garrido MJ et al. Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharmaceutical Research*, 2006, 23:2014–2023.

Kamel C. Tramadol en analgesia pédiatrica. *Revista Iberoamerican del Dolor*, 2008, 3:36–45.

Rose JB et al. Oral tramadol for the treatment of pain of 7–30 days' duration in children. *Anesthesia & Analgesia*, 2003, 96:78–81.

Codeine

Tremlett M, Anderson BJ, Wolf A. Pro-con debate: is codeine a drug that still has a useful role in pediatric practice? *Paediatric Anaesthesia*, 2010, 20:183–194.

Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. *British Journal of Anaesthesia*, 2001, 86:413–421.

Ibuprofen versus Codeine + Paracetamol

Drendel AL et al. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. *Annals of Emergency Medicine*, 2009, 54:553–560.

Morphine

Anderson BJ et al. The dose-effect relationship for morphine and vomiting after day-stay tonsillectomy in children. *Anaesthesia and Intensive Care*, 2000, 28:155–160.

Bhandari V et al. Morphine administration and short-term pulmonary outcomes among ventilated preterm infants. *Pediatrics*, 2005, 116:352–359.

Bouwmeester NJ et al. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *British Journal of Anaesthesia*, 2004, 92:208–217.

Koren G et al. Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *Journal of Pediatrics*, 1985, 107:963–967.

McNicol R. Postoperative analgesia in children using continuous s.c. morphine. *British Journal of Anaesthesia*, 1993, 71:752–756.

Saarenmaa E et al. Morphine clearance and effects in newborn infants in relation to gestational age. *Clinical Pharmacology and Therapeutics*, 2000, 68:160–166.

Zernikow B, Lindena G. Long-acting morphine for pain control in paediatric oncology. *Medical and Pediatric Oncology*, 2001, 36:451–458.

Fentanyl

Saarenmaa E, Neuvonen PJ, Fellman V. Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. *Journal of Pediatrics*, 2000, 136:767–770.

Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. *Canadian Journal of Anaesthesia*, 1987, 34:152–155.

Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology*, 1987, 66:433–435.

Fentanyl versus morphine

Saarenmaa E et al. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. *Journal of Pediatrics*, 1999, 134:144–150.

Adjuvants

Saarenmaa E et al. Ketamine for procedural pain relief in newborn infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 2001, 85:F53–F56.

ANNEX 5. RESEARCH AGENDA

The Guidelines Development Group established a research agenda in March 2010 while assessing the available evidence for pharmacological interventions as part of the process of developing recommendations. Having identified several research gaps, the GDG also discussed priorities for further investigation.

The list below ranks, in order of priority, the broad areas of research needed. This list aims to guide the scientific community in contributing to key research on pharmacological interventions for the management of persisting pain in children with medical illness. The outcomes measured in clinical studies comparing different pharmacological interventions should include both positive (efficacy, quality of life) and negative (incidence/prevalence and severity of adverse effects) outcomes.

First group of priorities

- Assessment of two-step treatment strategy.
- Research on alternative strong opioids to morphine (comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use).
- Research on intermediate potency opioid analgesics (e.g. tramadol).
- Long-term safety data concerning first-step medicines (ibuprofen/paracetamol).

Second group of priorities (neuropathic pain)

- Antidepressants, specifically tricyclic antidepressants and selective serotonin reuptake inhibitors and newer antidepressants of the class of serotonin and norepinephrine reuptake inhibitors for persisting neuropathic pain in children.
- Gabapentin for persisting neuropathic pain in children.
- Ketamine as an adjuvant to opioids for refractory neuropathic pain in paediatric patients with long-term medical illness.

Third group of priorities

- Randomized controlled trials of the administration of opioids as an alternative to the oral route (including RCTs comparing subcutaneous and intravenous routes).

Fourth group of priorities

- Update Cochrane reviews on opioid switching, including paediatric data, if available.
- Randomized controlled trials on opioid switching and research on dose conversion in different age groups.
- Randomized controlled trials on short-acting opioids for breakthrough pain in children.

Other areas for research and development

- Research and psychometric validation of observational behaviour measurement tools for persisting pain settings (neonates, infants, preverbal and impaired children).
- Prospective clinical trials to investigate opioid rotation policies and their efficacy in preventing side-effects or opioid tolerance and dose escalation.
- Development of divisible, dispersible, oral solid-dosage forms of paracetamol and ibuprofen.
- Research into appropriate formulations for the extemporaneous preparation of oral liquid morphine. Dissemination of available evidence on the preparation of stable extemporaneous formulations.
- Child-appropriate oral solid dosage forms of opioid analgesics.
- Research on dose conversion of opioid analgesics in different age groups.

ANNEX 6. OPIOID ANALGESICS AND INTERNATIONAL CONVENTIONS

This annex provides an overview of the main aspects linked to the procurement, supply and dispensing of opioid medicines and their status as controlled medicines under the United Nations Single Convention on Narcotic Drugs, 1961. It outlines the main requirements set by the Convention and their impact on operational and policy planning. This annex addresses policy-makers, managers, officers and health-care providers who are involved at different levels and in different functions with improving the availability of opioid analgesics for medical needs. It provides the principal references for further action and some general guidance on main regulatory aspects to be considered while improving access to opioid analgesics in the health system.

The World Health Organization published the policy guidelines *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines*, to guide countries how to optimize access to all controlled medicines and to prevent harm from substance misuse (*95*). The World Health Organization (WHO) encourages governments, civil society and other interested individuals to strive for the maximum public health outcome of policies related to these medicines. WHO considers the public health outcome to be at its maximum (or "balanced") when the optimum is reached between maximizing access for rational medical use and minimizing hazardous or harmful use. It is strongly recommended that countries implement these guidelines for achieving this outcome.

A6.1 UN 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* (*94*); the United Nations *Convention on Psychotropic Substances, 1971* (*119*); and the *United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988* (*120*). 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 medicines access.

The Commission on Narcotic Drugs (CND), which represents the States that are Parties to these international drug conventions, has the authority to decide, upon a recommendation from the World Health Organization, 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* (*121*). 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.

A6.2 The Single Convention on Narcotic Drugs and opioid analgesics

The *Single Convention on Narcotic Drugs, 1961*, as amended by the *1972 Protocol* (*94*) 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 among 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 considered for safe switching in children with persisting pain (fentanyl, hydromorphone, oxycodone and methadone) 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 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 premises, stocks and records are inspected;
- 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.*" Thus, this puts an obligation on the countries that are Parties to the international conventions to ensure the medical availability of the controlled substances.

A6.3 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. (*122*)

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 (*123*). A study on the adequacy of opioid consumption around the world concluded that 5 683 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 (*124*).

Drug control conventions were established to enhance public health, which is affected positively by the availability of controlled medicines for medical treatment and 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 mentioned earlier in this annex (*95*), in particular the Country Check List comprised in that publication.

A6.4 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 at:
http://www.painpolicy.wisc.edu/internat/countryprofiles.htm

A6.5 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 considered for safe switching in children with persisting pain) and Schedule II (*125*). 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 30th June, six months in advance of the period for which they apply. The Board 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 Board 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 Board informs the competent national authority of the country concerned of their estimates and requests the authority to review them.

A6.6 The importance of reliable estimates

The World Health Organization and the International Narcotics Control Board 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 only be used in the case of unforeseen circumstances and for the introduction of new treatments (*126*).

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.

A6.7 Domestic manufacture of strong opioid analgesics

After a country has received confirmation of its estimates from the INCB, it may start manufacturing or importing procedures for 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 record-keeping and security procedures, and 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 through 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;
- number of industrial establishments that will manufacture opioid medicines;
- quantities of opioid medicines to be manufactured by each establishment.

A6.8 The import/export system for strong opioids

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

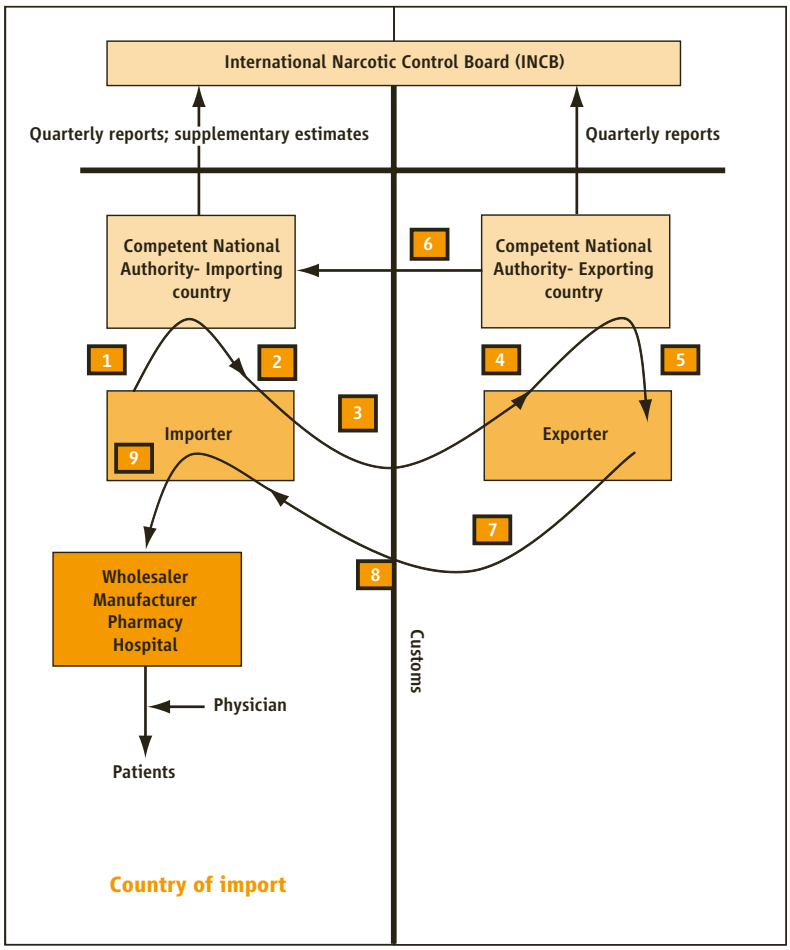
Generally, each country has its own importation procedures, which may require approval from different authorities in the country, such as the ministry of health, the national medicines regulatory authority and other entities (e.g. for import duties).

Specifically, the Single Convention requires additional steps and approvals for the importation and exportation of narcotic drugs. These steps, outlined below and in Figure A6.1 below, 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.[2]
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 and 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 to 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.
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.

[2] *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.*

Figure A6.1 Steps in opioid import/export procedures



See A6.8 for explanation of the numbered steps.

Source: (*127*)

A6.9 Requirements for import/export authorizations or certificates

Both import and export authorizations should include the:

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

The export authorization should also state the reference number and date of the import authorization, and 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 *Guidelines for the import and export of drugs and precursor references standards for use by national drug testing laboratories and competent national authorities* (*128*).

Import and export authorizations are normally required for each shipment.[3]

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.

A6.10 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 report the total amount of opioids manufactured, consumed and held in stock at 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.[4]

A6.11 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 for 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 record keeping. 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 increase distribution costs.

[3] *One import authorization can allow for more shipments (for which exportation authorization needs to be granted on a single basis).*

[4] *"Stock" is defined in Article 1 of the Single Convention on Narcotic Drugs 1961 as amended by the 1972 Protocol.*

A6.12 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:

- name and business address of the prescribing health professional
- name of the patient
- date of the prescription
- preparation to be dispensed (e.g. morphine tablet)
- dose to be dispensed in milligrams (words and numbers)
- frequency of dispensing (e.g. daily, twice daily)
- 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.

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A7.3 Declaration of interest and management of potential conflict of interest

All consultants, experts and contributors involved in the development of the guidelines were requested to declare any conflicts of interest. The management of conflicts of interest was a key task throughout the process, with particular attention being paid to the appraisal of evidence, the formulation of recommendations and the external peer review process of the drafted guidelines.

Declarations of interest by members of the Guidelines Development Group
Rae Bell declared that as a member of the editorial board of Smertefokus, the Pfizer pain publication, she receives Norwegian kroner (NOR) 12 000–16 000[5] per year. She declared receiving travel support from Pfizer. She also declared agreeing to receive an honorarium from the company Grünenthal for participating in meetings of the Nordic Expert Group on tapentadol. She declared to be technical adviser for pregabalin, marketed by Pfizer, in Norway. Tapentadol and pregabalin were not included among the medicines considered for clinical recommendations in these guidelines.

[5] *US$ 1 = NOK 5.75 (November 2011).*

Mariela Bertolino, declared having received US$ 5000 in a 2-year period from Archimedes Pharma Limited for a multicenter study of long-term safety on the use of fentanyl in the treatment of breakthrough cancer pain in adults.

Allen Finley declared being involved in research supported by several grants from the Canadian Institutes of Health Research, none of which entailed a personal financial benefit. He also declared his role as past-President of the Special Interest Group on Pain in Childhood of the International Association of Study of Pain (IASP). He declared having received US$ 3500 for technical consultation on study design for tramadol from Johnson & Johnson.

Henry Lu declared that he was technical adviser for pregabalin, marketed by Pfizer, in the Philippines. Pregabalin was not included among the medicines considered for clinical recommendations in these guidelines.

Rajat Ray declared having received support for post-marketing surveillance on Addnok-N (the combination of buprenorphine and naloxone) marketed by Rusan Pharma Ltd., India. Buprenorphine in combination with naloxone was not included among the medicines considered for clinical recommendations in these guidelines.

The other members of the Guidelines Development Group reported no conflicts of interest.

The GDG meeting was facilitated by Andy Gray and Nicola Magrini. Andy Gray reported being a Member of the Scheduling and Naming Expert Committee of the South African Medicines Control Council and trustee (Director) of LIFELab, the East Coast Biotechnology Regional Innovation Centre Trust, a government funding agency for biotechnology. LIFELab is not developing or producing any medicines considered for clinical recommendations in these guidelines. Both consultants reported no conflicts of interest.

Management of potential conflicts of interest of the members of the Guidelines Development Group

Allen Finley did not participate in a final decision on any recommendations related to tramadol. Mariela Bertolino did not participate in a final decision on any recommendations related to fentanyl.

Declaration of interest of the external reviewers

Rosa Buitrago reported being Product Patrimony Manager for Sanofi-Aventis in Panama from October 2007 to September 2010. No current interests reported.

Stuart MacLeod reported being the Director of the Child and Family Research Institute at British Columbia Children's Hospital from 2003 to January 2010. The institute has received around US$ 50 000 for research on pain from the private sector. No current interests reported.

Gary Walco reported having received payments from pharmaceutical companies for consultancies. These amounted to approximately: US$ 6500 from Purdue Pharma and US$ 2500 from Pfizer in 2010;

US$ 1500 from Neuromed in 2008; US$ 2000 from Anesiva and US$ 1000 from Endo in 2007; and US$ 2500 from Cephalon in 2006.

Boris Zernikow reported having received payments for consultancies from pharmaceutical companies of: approximately Euro 2000 from Reckitt Benckiser in 2007; Euro 2000 from Janssen in 2008; Euro 1500 from Wyeth in 2008; approximately Euro 20 000 from Grunenthal since 2008; and around Euro 1000 from Schwarz Pharma. He declared having received lecturer fees from several pharmaceutical companies since 2006 for a total of around Euro 16 000. He also declared having received congress sponsoring from several companies in 2007, 2009 and 2010, for a total of around Euro 116 000, and research support from several foundations.

The other external reviewers reported no conflicts of interest.

Management of potential conflicts of interest of the external reviewers

The comments provided by Rosa Buitrago, Stuart MacLeod, Gary Walco and Boris Zernikow related to improvement of the text and did not conflict with any recommendation and/or principle issued by the Guidelines Development Group.

SUMMARY OF PRINCIPLES AND RECOMMENDATIONS

Principles

Optimal pain management may require a comprehensive approach comprising a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacological strategies. A comprehensive approach is possible even in resource-limited settings.

Correct use of analgesic medicines will relieve pain in most children with persisting pain due to medical illness and relies on the following key concepts (pages 38–40):

- using a two-step strategy
- dosing at regular intervals ("by the clock")
- using the appropriate route of administration ("by the mouth")
- tailoring treatment to the individual child ("by the individual").

Clinical recommendations

1. It is recommended to use the analgesic treatment in two steps according to the child's level of pain severity. (pages 38, 84)
2. Paracetamol and ibuprofen are the medicines of choice in the first step (mild pain). (pages 38, 86)
3. Both paracetamol and ibuprofen need to be made available for treatment in the first step. (pages 38, 86)
4. The use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses. (pages 42, 87)
5. Morphine is recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses. (pages 42, 88)
6. There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice. (pages 42, 88)
7. Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability, including patient-related factors. (pages 42, 88)
8. It is strongly recommended that immediate-release oral morphine formulations be available for the treatment of persistent pain in children with medical illnesses. (pages 43, 90)
9. It is also recommended that child-appropriate prolonged-release oral dosage forms be available, if affordable. (pages 43, 90)
10. Switching opioids and/or route of administration in children is strongly recommended in the presence of inadequate analgesic effect with intolerable side-effects. (pages 44, 91)
11. Alternative opioids and/or dosage forms as an alternative to oral morphine should be available to practitioners, in addition to morphine, if possible. (pages 44, 91)
12. Routine rotation of opioids is not recommended. (pages 44, 91)
13. Oral administration of opioids is the recommended route of administration. (pages 45, 92)
14. The choice of alternative routes of administration when the oral route is not available should be based on clinical judgement, availability, feasibility and patient preference. (pages 45, 92)
15. The intramuscular route of administration is to be avoided in children. (pages 45, 92)

16. A careful distinction between end-of-dose pain episodes, incident pain related to movement or procedure, and breakthrough pain is needed. (pages 46, 94)

17. It is strongly recommended that children with persisting pain receive regular medication to control pain and also appropriate medicines for breakthrough pain. (pages 46, 94)

There is insufficient evidence to recommend a particular opioid or route of administration for breakthrough pain in children. There is a need to make an appropriate choice of treatment modality based on clinical judgement, availability, pharmacological considerations and patient-related factors. (pages 46, 94)

18. The use of corticosteroids as adjuvant medicines is **not** recommended in the treatment of persisting pain in children with medical illnesses. (pages 50, 95)

19. The use of bisphosphonates as adjuvant medicines is **not** recommended in the treatment of bone pain in children. (pages 50, 95)

At present, it is not possible to make recommendations:
- *for or against the use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) as adjuvant medicines in the treatment of neuropathic pain in children. (pages 51, 96)*
- *for any anticonvulsant as an adjuvant in the management of neuropathic pain in children. (pages 51, 97)*
- *regarding the benefits and risks of ketamine as an adjuvant to opioids for neuropathic pain in children. (pages 52, 98)*
- *regarding the benefits and risks of the systemic use of local anaesthetics for persisting neuropathic pain in children. (pages 52, 98)*
- *for the use of benzodiazepines and/or baclofen as an adjuvant in the management of pain in children with muscle spasm and spasticity. (pages 52, 99)*

Health system recommendations

20. Education of health professionals in the standardized management of persisting pain in children with medical illnesses and in the handling of the necessary medicines, including opioid analgesics, is encouraged. (pages 59, 101)

21. Health professionals will be allowed to handle opioids within their scope of practice or professional role based on their general professional licence without any additional licensing requirements. (pages 59, 101)

22. In addition, countries may consider, subject to their situation, allowing other professions to diagnose, prescribe, administer and/or dispense opioids for reasons of flexibility, efficiency, increased coverage of services and/or improved quality of care. (pages 59, 101)

23. The conditions under which such permission is granted should be based on the demonstration of competence, sufficient training, and personal accountability for professional performance. (pages 59, 101)

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