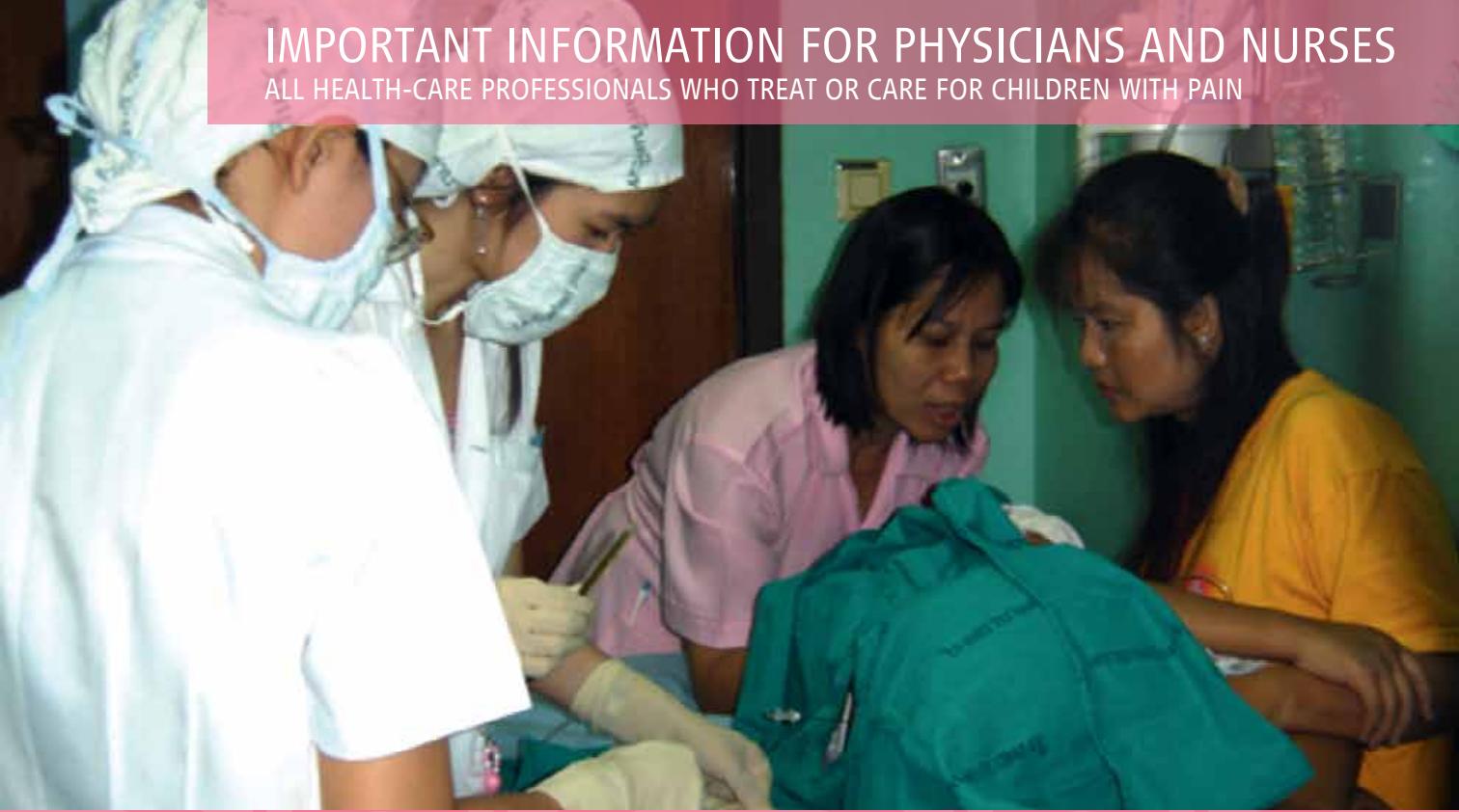


IMPORTANT INFORMATION FOR PHYSICIANS AND NURSES  
ALL HEALTH-CARE PROFESSIONALS WHO TREAT OR CARE FOR CHILDREN WITH PAIN



# Persisting pain in children

Highlights for physicians  
and nurses extracted  
from the *WHO guidelines  
on the pharmacological  
treatment of persisting  
pain in children with  
medical illnesses*



World Health  
Organization

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# Introduction

The brochure *Persisting pain in children* for physicians and nurses offers concise information which is extracted from the *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (1)* unless otherwise stated.

These new WHO guidelines outline basic principles, clinical recommendations and health system recommendations. This brochure highlights selected issues which are essential for all health-care professionals who treat or care for children with pain.

The *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses* address the pharmacological treatment of persisting pain, including cancer pain. As such, it replaces the previous guidelines *Cancer pain and palliative care in children*, which exclusively covered cancer pain. The new guidelines on persisting pain in children are the first of a series of three guidelines documents on all types of pain in both adults and children. The topics of the other two guidelines will be “persisting pain in adults” and “acute pain”. The basic principle of the guidelines is that all patients with pain, including children, should be treated with either pharmacological or non-pharmacological techniques, irrespective of whether the underlying cause can be identified.

The World Health Organization (WHO) estimates that around 5.7 billion people live in countries where moderate and severe pain is not adequately treated. Data from the International Narcotics Control Board (INCB) for 2009 show that more than 90 percent of the global consumption of strong opioids occurred in Australia, Canada, New Zealand, the United States of America, the United Kingdom and several other European countries. This means that their availability was very limited in many countries and regions. Over 80% of the world population will have insufficient analgesia.

Medicines for opioid analgesia, such as morphine, are subject to the international drug control conventions and as a result, the focus has historically been on prevention of misuse, dependence and diversion while medical access has been neglected. In recent years, growing recognition of the legitimate use of these substances for medical and scientific purposes has resulted in a shift in emphasis.

Mechanisms behind the impeded access to opioid analgesics and other controlled medicines are of various natures. They include legal and policy issues, and various educational issues at all levels, from patients and their families to physicians, pharmacists and policy-makers. Doctors and nurses have an important role to play in overcoming these barriers and expanding pain relief treatment to all patients who need treatment.

*This brochure provides background information on the treatment of pain in children that can be helpful to doctors and nurses for ensuring adequate access to pain treatment. For more detailed information and additional references we refer to the formal guidelines document. This formal guidelines document is available as hardcopy at the WHO Bookshop<sup>1</sup> and online at [www.who.int/medicines](http://www.who.int/medicines). In case of any discrepancy between this brochure and the guidelines document, the guidelines document should be the reference.*

Similar highlights brochures are published for pharmacists and policy-makers.

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<sup>1</sup> tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: [bookorders@who.int](mailto:bookorders@who.int); web: <http://apps.who.int/bookorders/>

**What is new**

**in the guidelines**





All patients with pain, including children, should be treated, 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 fabricated.

The new guidelines recommend using analgesic treatments in two steps according to the child's level of pain severity. Paracetamol and ibuprofen are the medicines of choice in the first step: the treatment of mild pain. In the second step, the treatment of moderate to severe pain, morphine is the medicine of choice. Correct use of analgesic medicines will relieve pain in most children with persisting pain due to medical illness.

In the new guidelines, WHO recommends that codeine and tramadol no longer be used for children. The effects of codeine are unpredictable because of intra-individual metabolic differences and therefore pose a safety risk. For tramadol, there is currently no available evidence for its comparative effectiveness and safety in children. In the previous guidelines, *Cancer pain and palliative care in children*, weak acting opioids like codeine and tramadol were recommended as an intermediate step between treatment with non-opioids paracetamol and ibuprofen and strong opioids like morphine.

Pethidine is now considered obsolete.

Practitioners should pay attention to the initial dosage of strong opioids. The dosages recommended by WHO are lower than those recommended elsewhere.

The term "persisting pain" as used in these guidelines is intended to cover long-term pain related to medical illness. "Medical illnesses" refers to specific situations of ongoing tissue damage where there is a clear role for pharmacological treatment.

# Recommended clinical approach





Optimal pain management begins with an accurate and thorough pain assessment. Following the assessment, a treatment plan is developed, including pharmacological and non-pharmacological interventions. This is then implemented and evaluated by a new assessment, with adjustment of the treatment plan as needed.

## PAIN ASSESSMENT

The pain assessment process involves the child, the parents or caregivers and the health-care providers. 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.

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, usually a pain intensity scale. Measurements should be recorded over time in the child's clinical chart or by the child or his/her caregivers in a journal.

Several questions that should be raised are presented in Table 1, below. The health-care provider should investigate the association of pain with any triggering factors by asking about any known aggravating and relieving factors. The health-care provider should also 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 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.

**Table 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.

The main behavioural indicators of acute pain are facial expression, body movement and body posture, inability to be consoled, crying and groaning. These behavioural responses may be reduced in persisting pain, except during acute exacerbations. Behaviour in children with chronic pain can include 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 and poor school performance.

However, children may display none of the expected clues. 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.

## PHARMACOLOGICAL TREATMENT

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:

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

### Using a two-step strategy

WHO recommends treating pain in two steps, based on pain severity assessment:

- Step 1 is for mild pain. The medicines used are non-opioid analgesics like paracetamol and ibuprofen. These substances have a fixed maximum dosage and can provide only limited analgesia.
- Step 2 is for moderate and severe pain. Strong opioids are used, e.g. morphine, using a weight-appropriate starting dose. The dosages recommended by WHO are lower than those recommended elsewhere. As long as the pain is not sufficiently addressed, the dosage needs to be increased in steps of no more than 50% per 24 hours.

### Dosing at regular intervals

Opioids should be administered at regular intervals and not on an “as-needed” basis.

### Using the appropriate route of administration

Although in many countries the prevailing route of administration is by injection, oral administration of opioids is preferred for all patients who are able to do swallow. The subcutaneous route could be a valuable alternative for other patients.

### Adapting treatment to the individual child

Treatment with strong opioids needs to be individually adjusted and there is no fixed maximum dosage. This may also include small rescue dosages in addition to the regular dosages for use in cases when additional pain is experienced (so-called “breakthrough pain”).

Alternative strong opioids may be needed instead in case a patient has dose-limiting side-effects to morphine. Several alternative strong opioids are discussed in the pharmacological profiles on page 23.

## OTHER ASPECTS TO CONSIDER WHILE TREATING PAIN IN CHILDREN

### Long-term opioid use

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

### Weaning

Patients can wean from opioids safely in 5–10 days after short-term therapy without posing significant health risks. After long-term therapy the weaning period will take weeks. The occurrence of withdrawal syndrome needs to be monitored and if necessary the tapering off needs to be slowed down.

### Antidote

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.

*It is recommended for physicians and nurses to read the entire Chapters 1, 2 and 3 of the new WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, which deal with classification of pain in children, evaluation of persisting pain in the paediatric population and pharmacological treatment strategies.*

# Health system recommendations

# 3



Opioid analgesics such as morphine and pain management services should be available at all levels of care. Therefore, the competence to prescribe controlled medicines, including strong opioids, should not be restricted to a small number of medical specialties, e.g. oncologists or HIV specialists only.

### **Need for education and training**

The prescription of opioid analgesics is similar to the prescription of most other medicines. When used rationally for medical purposes, strong opioids are safe medicines. However, certain limitations need to be taken into account as described under Section 2, *Recommended clinical approach*, in particular the maximum daily increase and the importance of weaning gradually. Therefore training and education on how to prescribe opioids is very important.

***For methadone, additional training on the dosage is important as it has a long half-life in the body and tends to accumulate, with a risk of overdosage.***

Assessment and measurement of pain is essential for estimating pain severity, and hence, for deciding which medicine to prescribe or how to adjust the dosage. Therefore, education in the assessment of pain, in particular in children, is also important. Children often show their pain in a different way than adults, and therefore their pain may be not recognized.

### **Use of morphine oral solution**

Some countries with extremely low resources for health care use morphine oral solution, which is locally prepared by the pharmacy for direct use. By using morphine sulphate or hydrochloride powder as the starting material, the cost per patient can be as low as USD 0.05 a day. Expiry dates should be regularly checked and respected.

### **Importance of estimating needs for pain relief**

Every year, the national authorities must prepare estimates for the following calendar year of their requirements for morphine and other strong opioids. This is a particularly important step in the supply cycle of opioid analgesics as it is a prerequisite for the uninterrupted supply of these essential medicines. Although the production of estimates is a government responsibility, when requested, input from local health-care professionals will be essential to produce accurate estimates.

### **Situational analysis**

A crucial step towards expanding pain relief treatment in the health system is to assess the national system with regards to factors that impede access to treatment, such as regulations restricting the availability or accessibility of opioid analgesics. Countries that have very strict laws and policies that do not allow ready access to pain treatment should endeavour to make them less restrictive and more practicable. The World Health Organization has developed guidelines that elaborate on the policy aspects of improving access to ensure the balance between the adequate availability for medical and scientific purposes while simultaneously preventing abuse, diversion and trafficking (2). It is one of the roles of all health-care workers to bring undue restrictions for access to pain treatment services to the attention of the authorities.

Special

issues

4





This section addresses special issues that need to be taken into account in improving access to pain relief.

### **Risk of dependence**

Dependence is not merely the occurrence of tolerance and withdrawal symptoms. According to the definition of dependence syndrome, other symptoms need to exist, including a strong desire to take a substance, difficulties in controlling its use, persisting in its use despite harmful consequences, and a higher priority given to substance use than to other activities and obligations (ICD-10 definition).

Withdrawal can be prevented by gradually reducing the dose instead of making an abrupt interruption. Tolerance (a need for higher doses in order to achieve the same effect) may also occur with opioid analgesics, although the need for a higher dosage may also be related to an increased severity of the disease and the pain.

Prevalence of the dependence syndrome in pain patients is rare. The possibility that dependence might occur should not be a reason for not addressing the patient's pain, and when there is no further need for pain treatment, the dependence should be addressed, just like any other side-effect of the pain treatment should be treated.

### **Risk of diversion**

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.

### **Sudden interruption of supply of strong opioid medicines**

Sudden interruption of treatment with strong opioids leads to severe withdrawal syndrome. Signs and symptoms of the opioid withdrawal syndrome may include yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils, piloerection, chills, tachycardia, hypertension, nausea and vomiting, cramping abdominal pains, diarrhoea, and muscle aches and pains. Withdrawal can cause additional suffering, and therefore it is extremely important to ensure the quality of the procurement system in order to minimize the risk of interruptions.

### **Research agenda**

Many aspects of the pharmacological treatment of pain in children are insufficiently investigated. For this reason the guidelines development group of experts that developed these guidelines recommended a research agenda with priority topics for research in this area.

*It is recommended for physicians, nurses and pharmacists who conduct research to read Annex 5 of the guidelines, Research agenda.*

### **Formulas for morphine oral solution**

Considerable savings can be achieved by compounding an oral solution in the pharmacy as opposed to buying commercial preparations. Oral solutions can be made using morphine sulphate or morphine hydrochloride powder. When selecting a formula for oral morphine solution, the biological and chemical shelf-life should be considered. The preservation is in particular important. Several circulating formulas use carcinogenic or ineffective ways of preservation, such as with bronopol (2-bromo-2-nitropropane-1.3-diol) or chloroform water.

WHO recommends using formulas with safe ingredients only, an effective preservation and an established biological and chemical shelf-life. An example of such a formula is the Oral Morphine Solution from the Formulary of the Dutch Pharmacists (FNA). A modified version is included in the WHO highlights brochure *Persisting pain in children: important information for pharmacists*.

# Annex 1

## Content of the document *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*

This brochure is extracted from the *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*. In order to give the reader an impression of the main document, its content is summarized below.

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. 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.

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.

The **Introduction** states the objective of these guidelines and 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, emphasizing that 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.

**Chapter 4.** *Improving access to pain relief in health systems* sets out a number of considerations regarding how to improve access to pain treatment and includes four policy recommendations.

**Annex 1.** Provides *Pharmacological profiles* for selected medicines. **Annex 2.** *Background to the clinical recommendations*, gives a description of the development process of the 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 by the Guidelines Development Group when formulating the recommendations from Chapter 4. **Annex 4.** *Evidence retrieval and appraisal*, presents the GRADE tables which were developed for using the retrieved literature, and the observational studies that were retrieved on topics for which there were no systematic reviews and randomized clinical trials. **Annex 5.** outlines the *Research agenda*. International requirements for the handling and procurement of morphine and other opioid analgesics for the relief of pain are described in **Annex 6**. Finally, in **Annex 7**, individuals who contributed to the guidelines are listed.

# Annex 2

## Dosage tables for quick reference

(see also the pharmacological profiles)

**Table 2** Starting dosages for opioid analgesics for opioid-naïve neonates

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

<sup>a</sup> Administer IV morphine slowly over at least 5 minutes.

<sup>b</sup> The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.

<sup>c</sup> Administer IV fentanyl slowly over 3– 5 minutes.

**Table 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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>b</sup>	IV injection	1–2 mcg/kg every 2–4 hrs <sup>c</sup>
	IV infusion	Initial IV dose 1–2 mcg/kg <sup>c</sup> , then 0.5–1 mcg/kg/hr
Oxycodone	Oral (immediate release)	50–125 mcg/kg every 4 hrs

<sup>a</sup> Administer IV morphine slowly over at least 5 minutes.

<sup>b</sup> The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.

<sup>c</sup> Administer IV fentanyl slowly over 3–5 minutes.

**Table 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 <sup>a</sup>	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 <sup>a</sup> , then 20–30 mcg/kg/hr
	SC infusion	20 mcg/kg/hr
Fentanyl	IV injection	1–2 mcg/kg <sup>b</sup> , repeated every 30–60 minutes
	IV infusion	Initial IV dose 1–2 mcg/kg <sup>b</sup> , then 1 mcg/kg/hr
Hydromorphone <sup>c</sup>	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)
	IV injection <sup>d</sup> or SC injection	15 mcg/kg every 3–6 hrs
Methadone <sup>e</sup>	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) <sup>f</sup>
	IV injection <sup>g</sup> and SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hrs (max 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hrs

<sup>a</sup> Administer IV morphine slowly over at least 5 minutes.

<sup>b</sup> Administer IV fentanyl slowly over 3–5 minutes.

- <sup>c</sup> 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.
- <sup>d</sup> Administer IV hydromorphone slowly over 2–3 minutes.
- <sup>e</sup> 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.
- <sup>f</sup> 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%.
- <sup>g</sup> Administer IV methadone slowly over 3–5 minutes.

**Table 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 <sup>a</sup>
Methadone	1:1–1:2

- <sup>a</sup> 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.

# Annex 3

## Preparations

### **Preparation availability**

For providing adequate pain treatment the following preparations need to be available:

### **Step 1 analgesics (non-opioids)**

*For step one both paracetamol and ibuprofen should be available.*

#### **Paracetamol**

Oral liquid: 25 mg/ml.  
Suppository: 100 mg.  
Tablet: 100–500 mg.

#### **Ibuprofen**

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

### **Step 2 analgesics (strong opioids)**

*Morphine should always be available as immediate release dosage forms (oral liquid, immediate release (IR) tablets 10 mg and injections). Additionally, prolonged release tablets and granules should be available if affordable.*

#### **Morphine**

Oral liquid: 2 mg (as hydrochloride or sulfate)/ml.  
Tablet: 10 mg (as sulfate).  
Injection: 10 mg (as hydrochloride or sulfate) in 1 ml ampoule.

Tablet (prolonged release): 10 mg, 30 mg, 60 mg, 100mg, 200mg (as sulfate).  
Granules: (prolonged release, to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).

*Additionally, one or more other strong opioids should be available as an alternative to morphine in step two. There are many options, including:*

#### **Fentanyl**

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).

**Hydromorphone**

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.

**Methadone (WARNING: requires additional training for dosing)**

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).

**Oxycodone**

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

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

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

Oral liquid: 1 mg/ml (as hydrochloride).

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

*The use of **pethidine** is not recommended.*

**Antagonist**

*For use in opioid overdosage*

**Naloxone**

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

# Annex 4

## Pharmacological profiles

*Please see Annex 1 of the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses for further details on interactions with other medicines.*

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. 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.

### A4.1 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-naïve 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.

**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 > 700 micromol/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, beta-adrenergic blockers, calcium channel blockers, central nervous system depressants, imidazole antifungals, macrolide antibiotics, monoamine oxidase inhibitors\*, naloxone\*, naltrexone\*, neuroleptics, nitrous oxide, opioid antagonists/partial agonists, phenytoin, protease inhibitors.

\* 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.*

## A4.2 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-naïve 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.

**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, ethanol\*, monoamine oxidase inhibitors\*, naloxone\*, naltrexone\*, opioid antagonists/partial agonists\*.

\* 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.

### A4.3 Ibuprofen

**ATC code:** M01AE01

**Tablet:** 200 mg, 400 mg.

**Oral liquid:** 100 mg/5 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 10–20 mL/min or serum creatinine 300–700 micromol/L) to severe (GFR <10 mL/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\*, cyclosporin\*, dexamethasone, digoxin, enalapril, fluoxetine\*, furosemide, heparin, hydrocortisone, levofloxacin\*, lithium\*, methotrexate\*, ofloxacin\*, penicillamine, phenytoin\*, prednisolone, propranolol, ritonavir, spironolactone, warfarin\*, zidovudine.

\*Indicates severe.

**Notes:**

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

**A4.4 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).

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**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.

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**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-naïve 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.

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

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

### Adverse effects:

- **common** – nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, drowsiness, muscle rigidity, hypotension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dependence, confusion, urinary retention, ureteric spasm;
- **uncommon** – restlessness, dyspnoea, hypoventilation, 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, amiodarone, atomoxetine, carbamazepine, central nervous system depressants, efavirenz, fluvoxamine, fosamprenavir, medicines that prolong the QT interval, monoamine

oxidase inhibitors\*, naloxone\*, naltrexone\*, nelfinavir, nevirapine, opioid antagonists/partial agonists, phenobarbital, phenytoin, quinine, rifampicin, ritonavir, voriconazole, zidovudine.

\* 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.

## A4.5 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-naïve 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.

**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, chlorpromazine, ciprofloxacin, diazepam, haloperidol, metoclopramide, naloxone\*, naltrexone\*, opioid antagonists/partial agonists, ritonavir\*.

\* 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.

## A4.6 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 opioids and/or their active metabolites (codeine, dextropropoxyphene, dihydrocodeine, morphine, pethidine, oxycodone) is delayed in impairment so these opioids will accumulate; extended treatment with naloxone infusion may be required to reverse opioid effect.

**Hepatic impairment:** no dose adjustment necessary.

**Adverse effects:**

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

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

**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.

## A4.7 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-naïve 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.

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

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

**Adverse effects:**

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

**Interactions with other medicines:**

central nervous system depressants, monoamine oxidase inhibitors\*, naloxone\*, naltrexone\*, opioid antagonists/partial agonists\*.

\* 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.

## A4.8 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, metoclopramide, phenobarbital, phenytoin, warfarin

### 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.

## 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:

- 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.
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.
4. The use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses.
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.
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.
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.
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.

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.

*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.*

18. The use of corticosteroids as adjuvant medicines is **not** recommended in the treatment of persisting pain in children with medical illnesses.
19. The use of bisphosphonates as adjuvant medicines is **not** recommended in the treatment of bone pain in children.

*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.*
- *for any anticonvulsant as an adjuvant in the management of neuropathic pain in children.*
- *regarding the benefits and risks of ketamine as an adjuvant to opioids for neuropathic pain in children.*
- *regarding the benefits and risks of the systemic use of local anaesthetics for persisting neuropathic pain in children.*
- *for the use of benzodiazepines and/or baclofen as an adjuvant in the management of pain in children with muscle spasm and spasticity.*

### 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.
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.

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World Health Organization  
20 Avenue Appia  
CH-1211 Geneva 27

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