
CHAPTER 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 recommendations 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 threestep 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.


For topics/annex referred outside Chapter 3, see complete copy of WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses available on the WHO website.
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.

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

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose (oral route)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracetamol</strong></td>
<td>5–10 mg/kg every 6–8 hrs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>5–10 mg/kg every 6–8 hrs</td>
</tr>
</tbody>
</table>

*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.

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.

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

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route of administration</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td>Oral (immediate release)</td>
<td>80–200 mcg/kg every 4 hrs</td>
</tr>
<tr>
<td></td>
<td>IV injection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1–6 months: 100 mcg/kg every 6 hrs</td>
</tr>
<tr>
<td></td>
<td>SC injection</td>
<td>6–12 months: 100 mcg/kg every 4 hrs (max 2.5 mg/dose)</td>
</tr>
<tr>
<td></td>
<td>IV infusion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>SC infusion</td>
<td>1–3 months: 10 mcg/kg/hr 3–12 months: 20 mcg/kg/hr</td>
</tr>
<tr>
<td><strong>Fentanyl</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IV injection</td>
<td>1–2 mcg/kg every 2–4 hrs&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>IV infusion</td>
<td>Initial IV dose 1–2 mcg/kg, then 0.5–1 mcg/kg/hr</td>
</tr>
<tr>
<td><strong>Oxycodeine</strong></td>
<td>Oral (immediate release)</td>
<td>50–125 mcg/kg every 4 hours</td>
</tr>
</tbody>
</table>

*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.

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**Note:** 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.
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 necessary, 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 postoperative 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 dose 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: meperidine) should no longer be used, because it is considered inferior to morphine due to its toxicity on the central nervous system (74).

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

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route of administration</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Oral (immediate release)</td>
<td>1–2 years: 200–400 mcg/kg every 4 hrs 2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg)</td>
</tr>
<tr>
<td></td>
<td>Oral (prolonged release)</td>
<td>200–800 mcg/kg every 12 hrs</td>
</tr>
<tr>
<td></td>
<td>SC injection</td>
<td>2–12 years: 100–200 mcg/kg every 4 hrs</td>
</tr>
<tr>
<td></td>
<td>SC infusion</td>
<td>SC infusion 20 mcg/kg/hr</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV injection</td>
<td>1–2 mcg/kg, repeated every 30–60 minutes</td>
</tr>
<tr>
<td></td>
<td>IV infusion</td>
<td>Initial IV dose 1–2 mcg/kg, then 1 mcg/kg/hr</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral (immediate release)</td>
<td>30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)</td>
</tr>
<tr>
<td></td>
<td>IV injection or SC injection</td>
<td>15 mcg/kg every 3–6 hrs</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral (immediate release)</td>
<td>100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially)</td>
</tr>
<tr>
<td>Oxy-</td>
<td>Oral (immediate release)</td>
<td>125–200 mcg/kg every 4 hours (max 5 mg/dose)</td>
</tr>
<tr>
<td>codone</td>
<td>Oral (prolonged release)</td>
<td>5 mg every 12 hours</td>
</tr>
</tbody>
</table>

* Administer IV morphine slowly over at least 5 minutes.
* Administer IV fentanyl slowly over 3–5 minutes.
* 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.
* Administer IV hydromorphone slowly over 2–3 minutes.
* 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.
* 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%.
* Administer IV methadone slowly over 3–5 minutes.

### 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*
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.

**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).

**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).

**3.8 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).

**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).

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose ratio (parenteral : oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1:2 – 1:3</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1:2 – 1:5*</td>
</tr>
<tr>
<td>Methadone</td>
<td>1:1 – 1:2</td>
</tr>
</tbody>
</table>

* 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.

### 3.10 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 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
and children who are opioid-tolerant, naloxone needs to
thereafter to maintain wakefulness until the adverse effect
low-dose infusion under close monitoring may be required
starting at 1 microgram (mcg)/kg are titrated over time,
e.g. every 3 minutes, until the necessary dose is found. A
withdrawal syndrome. Moderate opioid overdose can be
classical sign of pinpoint pupils – which can lead to
respiratory depression–usually accompanied by the
When opioid overdose occurs, the child may have
experience opioid withdrawal syndrome if it is suddenly
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
efforts 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
on the safety and efficacy of bisphosphonates in children.

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 (B71).

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-

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

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>18. The use of corticosteroids as adjuvant medicines is not recommended in the treatment of persisting pain in children with medical illnesses.</td>
</tr>
<tr>
<td>Weak recommendation, very low quality of evidence</td>
</tr>
</tbody>
</table>

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

<table>
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<tr>
<th>Recommendation</th>
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<tr>
<td>Weak recommendation, very low quality of evidence</td>
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</table>

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 (B22). 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 antidepressants, 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 antidepressants are well described. In adults, adverse effects with tricyclic antidepressants 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 anticonvulant 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 persistent 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.
### Index of Drugs Related to the Guideline

This index lists the products of interest and/or their therapeutic classifications related to the guideline. This index is not part of the guideline. For the doctor’s convenience, brands available in the PPD references are listed under each of the classes. For drug information, refer to the PPD references (PPD, PPD Pocket Version, PPD Text, PPD Tabs, and www.TheFilipinoDoctor.com).

#### Non-Opioid Analgesics

**Paracetamol**
- Aeknil
- Alaxan
- Alvedon
- Biogesic
- Calpol
- Dolexpar
- Kiddiets
- Nahalgesicx
- Norgesic
- Opigesic
- Pynal
- Rexidal
- Sinomol
- Tempra/Tempra Forte
- Tylenol

**NSAIDs**
- Ibuprofen
  - Advil
  - Doloan FP
  - Faspic
  - Medical Advance
  - Medical I-400
  - Midol
  - Mutrim

**Opioid Analgesics**
- Fentanyl
  - Durogesic D Trans
  - Sublimaze
- Morphine sulfate
  - Hicon Morphine Sulfate
  - MST Continus
- Oxycodone
  - Oxycontin
  - Oxynorm
  - Oxynorm Injection
- Oxycodone/Naloxone
  - Targin
- Hydromorphone
  - Jurnista
- Methadone

**Antidotes**
- Naloxone

**Adjuvants**

**Tricyclic Anti-depressants (TCAs)**
- Amitriptyline
- Nortriptyline

**Selective serotonin reuptake inhibitors (SSRIs)**
- Fluoxetine
  - Adepasir
  - Drafzin
  - Motivate
  - Prod
  - Prozac 20
  - Prozyn

**Anti-convulsants**
- Carbamazepine
  - Carbilepp
  - Epazin/Epazin CR 200
  - Mezacar 200 mg/Mezacar SR
  - Tegretol
  - Zynaps
- Gabapentin
  - Calmepent
  - Gaba-100/Gaba-300
  - Gabalion-300
  - Gabatin
  - Gabix
  - Neurontin
  - Reinin
  - Zycha

**Anesthetics**
- Ketamine
  - Ketamax
- Lidocaine
  - Elin Lidocaine HCl 2% Inj
  - Hospira Lidocaine HCL (Premixed)
- Moxiletine

**Skeletal Muscle Relaxants**
- Baclofen
  - Lioresal
  - Onelaxant-R

**Hypnotic/Sedative**
- Benzodiazepines
  - Alprazolam
    - Altrax 250/500
    - Axal
    - Xanor
    - Xanor XR
  - Bromazepam
    - Lexotan
  - Clonazepam
    - Clonotril-0.5/2
    - Rivotril
  - Clorazepate
    - Tranxene
  - Diazepam
    - Tranxil
    - Vialum
  - Estazolam
    - Esilgan
  - Flurazepam
  - Lorazepam
  - Midazolam
    - Dormicum
    - Hypozam
    - Sedoz
  - Nitrazepam