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REVIEW ARTICLE

Pain management in children

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Abstract

The paediatric population is at risk of inadequate pain management, with age-related factors affecting pain management in children. This presented study discusses the complexities of measuring paediatric pain, reviews the most well-known pain assessment scales, and emphasizes the importance of family involvement in situations where children are asked to self-report their experiences. Current recommendations for treatment of pain in children are critically reviewed.

Key words

pain, children, pain management

INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' [1]. It is important to stress that pain encompasses both peripheral physiologic and central cognitive/emotional components and may or may not be associated with real tissue damage. Pain may exist in the absence of demonstrable somatic pathology. The assessment of pain, therefore, relies largely upon the use of self-report. An even more difficult and complex issue is the identification, measurment, and effective treatment of pain in children [2].

Categories of paediatric pain. Typically, paediatric pain can be divided into three major categories, i.e.: somatic, visceral and neuropathic [3]. Somatic pain is caused by tissue injury or inflammation. Typical examples of somatic pain include burns, fractures, infections, and various inflammatory conditions. When involving skin and superficial structures, somatic pain is sharp and well-localized. Visceral pain is caused by inflammation or injury of internal organs (viscera), usually poorly localized or referred to distant locations. Typical examples include appendicitis, rapidly increasing hepatomegaly, bowel distension or gastritis. Finally, neuropathic pain is caused by injury, inflammation, or dysfunction of the peripheral or central nervous systems, e.g. associated with phantom limb pain, Guillain-Barré syndrome, sciatica, etc.

Pain from the public health perspective. Pain among children and adolescents has been identified as an important public health problem, although little is known about the epidemiology of pain in children. It is estimated that 15–25% of children and adolescents suffer from recurrent or chronic pain. More than 50% of them have experienced a pain episode within the previous 3 months. The prevalence of chronic pain increases with age, and is more common in girls than boys. Girls are significantly more likely to report multiple health complaints. This tendency was also shown in international studies and proved in almost all countries and regions [4, 5, 6, 7]. Gender differences in prevalence increase with age. In the majority of countries and regions, girls at the age of 15 present a more than 10% higher burden of health complaints than boys. The most common types of complaints are abdominal pains, musculoskeletal pain, and headaches. Health complaints of somatic performance and psychological symptoms, e.g. nervousness or irritability, tend to occur together. Episodes of pain impact on school performance and peer relations. Recurrent pain is a reason for more than a half of short-period (1–6 days) school absences. Children with recurrent pains are at risk to develop additional physical and mental problems, such as functional disorders and anxiety in adulthood. 25–50% of patients with recurrent functional pains in adolescence continue to suffer from this condition in adulthood. Approximately 35% of patients with recurrent pains in childhood develop some psychiatric problems in adulthood [8, 9, 10].

The burden of frequent stress imposes the development of pain complaints. There is much evidence for the association of recurrent pain with family conflicts, experience of violence, bullying, lack of acceptance by peers, and lack of proper support from parents and teachers. In an HBSC study, school has been identified as a protective factor against multiple health complaints. However, low perceived classmate support is related to presentation of headaches and abdominal pains. The presence of recurrent pains in adolescents varies within the social gradient. The family lack of affluence, especially the poor social status predicts more risk of development of pains [4, 11, 12, 13].

Recurrent pain in children is also one of most common reasons for paediatric consultations. However, recurrent pains are in the majority of benign causation, they result in additional diagnostics, specialist consultations, which may elevate anxiety and impression of suffering from a serious condition. In turn, differential diagnostics of recurrent pains may immensely elevate stress in children and parents and aggravate symptoms. There is a need to seek an organic background for the causes of pain, with its increased health expenditure and overtreatment.

Pain assessment. Until recently, many believed that neonates experienced no pain or less pain than adults, children, or

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infants who underwent similar surgical procedures. However, only within the last two decades medical professionals has realized that all paediatric patients, including neonates, also feel pain and require relevant medical intervention [2, 3]. There is no consensus of opinion about when a foetus begins to experience pain. Most opinions range from 26 – 30 weeks of gestation [4]. Van de Velde and de Buck [5] have described that the peripheral receptors develop from the 7th gestational week, and from 20 weeks' gestation peripheral receptors are present in the whole body. In their opinion, the development of afferent fibres connecting peripheral receptors with the dorsal horn starts at 8 weeks' gestation, while thalamocortical connections are present from 17 weeks' and are completely developed at 26–30 weeks' gestation [5].

Gupta et al. [6] suggest that probably the brain stem in early gestation may perform some neurological functions that are subsequently subsumed by the cortex. During early gestation, the foetus reacts to stimuli to pain receptors in various ways. In some studies, foetal stress responses have been detected; however, this needs further research to define its significance. Stress reduction is certainly beneficial for children, and the same would presumably apply to foetuses; this may well have implications for foetal surgery [7, 8]. Perhaps, with the mother's consent, foetuses at risk of experiencing pain should be given appropriate doses of regional anaesthesia or analgesia, according to clinical circumstances [8, 9].

There is no evidence to support the view that pain is less intense in neonates and young children due to their developing nervous system [2]. On the other hand, pain is subjective and the pain response is individual and modified through various experiences during life [2, 9]. Some studies suggests that childhood pain response is more intense at the beginning and diminishes much earlier than in adults [2, 10]. Because the etiology of childhood pain is also highly emotional, therefore the understanding and help of parents are very required [11].

Pain means significant stress in all paediatric patients, and is associated with an inferior medical outcome. Young infants who during surgery received inadequate treatment for pain, produce enormous amounts of stress hormones, which results in increased catabolism, immunosuppression and haemodynamic instability [3, 12]. Thus, younger children may even experience higher levels of distress during painful procedures that older children, because they tend to cope with pain more behaviourally [3, 12].

Pawar and Garten [2] have described developmental differences of pain expression in such various paediatric age groups:

- Infants – may exhibit body rigidity, may include arching, exhibit facial expression (brows lowered and drawn together, eyes tightly closed, mouth open and squarish), cry intensely/loudly, draw knees to chest, exhibit hypersensitivity or irritability, have poor oral intake, or be unable to sleep.
- Toddlers – may be verbally aggressive, cry intensely, exhibit regressive behaviour or withdraw, exhibit physical resistance by pushing painful stimulus away after it is applied, guard painful area of body, or be unable to sleep.
- Preschoolers – may verbalize intensity of pain, see pain as punishment, exhibit thrashing of arms and legs, attempt to push a stimulus away before it is applied, be uncooperative, need physical restraint, cling to a parent, nurse, or other guardian, request emotional support, understand that there can be secondary gains associated with pain, or be unable to sleep.
- School-age children – may verbalize pain, use an objective measurement of pain, be influenced by cultural beliefs, experience nightmares related to pain, exhibit stalling behaviours, have muscular rigidity, e.g. clenched fists, white knuckles, gritted teeth, contracted limbs; exhibit body stiffness, closed eyes, wrinkled forehead, engage in the same behaviours listed for pre-schoolers/young children, or be unable to sleep.
- Adolescents – may localize and verbalize pain, deny pain in the presence of peers, have changes in sleep patterns or appetite, be influenced by cultural beliefs, exhibit muscle tension and body control, display regressive behaviour in the presence of the family, or be unable to sleep.

Age-specific and developmentally specific measures. Because infants, young children, and non-verbal children cannot express the quantity of pain they experience, several pain scales have been devised in an attempt to quantify pain in these populations [14, 15]

Newborn and infant. A range of behavioural distress scales were developed for the newborn and infant were, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Typical facial signs of pain and physical distress in infants are: eyebrows lowered and drawn together, a bulge between the eyebrows and vertical furrows on the forehead, eyes slightly closed, cheeks raised, nose broadened and bulging, deepened nasolabial fold, open and squarish mouth [2, 3, 10]. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxaemia, and cardiac or renal dysfunction [2, 3, 12, 13]. The most commonly used scales in newborns are the Premature Infant Pain Profile (PIPP) and the CRIES Postoperative Pain Scales [16–18]. The FLACC (Face, Legs, Activity, Cry and Consolability) Scale is a behavioural scale that has been validated for assessment of postoperative pain in children between the ages of 2 months and 7 years [19].

After observing a child for one to five minutes, a pain score is obtained by reviewing the descriptions of behaviour and selecting the number that most closely matches the observed behaviour.

Pre-school infants. Children 3–6 years old become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas; referral of hip pain to the leg or knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded colour intensities [2, 3, 13, 20].

Well established self-report pain scales developed for young children include the Poker Chip Scale, Wong-Baker Faces Scale (free to use), the Faces Pain Scale-Revised (FPS-R) and the Oucher Scale [20, 21, 22, 23, 24, 25] The FPS-R has been translated into more than 30 languages and is also free to use [21]. The Oucher Scale, available in different ethnic versions, permits children to rate their pain intensity by matching it to photographs of other children's faces depicting increasing levels of pain, and is well accepted in children over

6 years of age [3, 25, 26, 27, 28, 29]. The Poker Chip Scale asks children to quantify their pain in 'pieces of hurt', with more poker chips representing more pain. Body outlines allow young children to point to the location of their pain. The Poker Chip Tool appears to have the most utility as a simple clinical assessment tool to identify presence/absence of pain and general estimates of pain intensity in young children [3, 29, 30, 31, 32, 33, 34, 35, 36].

School-children and adolescents. In this age group, children can usually use verbal scales or visual analog pain scales (VASs) accurately. The VASs is the gold standard for assessment of pain in adults. The traditional scale is a 10cm scale with markings at 1 cm intervals from 0 – 10. Zero denotes 'no pain' and 10 denotes 'excruciating pain'. The patient is asked to identify the mark on the scale that corresponds to his/her degree of pain. The Numerical Rating Scale (NRS) consists of numbers from 0 – 10, in which 0 represents no pain and 10 represents very severe pain. This scales valid and reliable ratings are for children of 8 years and older. There is debate about the label for the highest pain rating, but the current agreement is not to use the worst pain possible, because children can always imagine a greater pain. Pain scores do not always correlate with changes in heart rate or blood pressure [31, 32, 33, 34, 35, 36, 37, 38, 39].

Cognitively impaired children. Measuring pain in cognitively impaired children remains very difficult. Understanding pain expression and experience in this population is important, because behaviours may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than cognitively competent children. Hennequin et al [40] stated that Down syndrome children may express pain less precisely and more slowly than the general population, whereas Bandstra et al [42] reported that pain in children with autism spectrum disorders may be difficult to assess because they may be both hyposensitive and hypersensitive to many different types of sensory stimuli, and they may have limited communication abilities. Self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. For assessment pain for this group of children the Non-communicating Child's Pain Checklist – Postoperative Version is recommended. Maladaptive behaviour and reduction in functions may also indicate pain. Children with severe cognitive impairments experience pain frequently, mostly not because of accidental injury. Children with the fewest abilities experience the most pain [3, 42].

Paediatric pain management. Pain management in children should follow the WHO analgesic stepladder ('be the ladder'), be administered on a scheduled basis ('by the clock'), because 'on demand' often means 'not given'), be given by the least invasive route ('be the mouth'), and tailored to the individual child's circumstance and needs ('be the child') [43]. Although there is a limited number of analgesic medicines that can be safely used in children, the WHO recommends in its last guidelines the provision of 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 [43]. Both pharmacologic and non-pharmacologic approaches to pain management should be considered for all pain treatment plans. Many simple interventions designed to promote relaxation and patient control can be expected to work synergistically with pain medications for optimal relief of pain and related distress. Psychological and developmental comorbidities affect the child's experience of pain and ability to tolerate and cope with it. Therefore, it is important to assess a child for evidence of situational anxiety and/or anxiety disorders. All psychological and developmental comorbidities should be determined and addressed, to adequately treat the child in pain or to reduce the risk of the child's developing ongoing pain after surgery, trauma, or even invasive medical procedures [4, 11, 13]. Therefore, in many paediatric centres, special paediatric pain services have been established [44, 45]

Non-pharmacological methods which can be used to relieve pain, fear, and anxiety in children [43]:

- emotional support (parents should be with their child during any painful procedures);
- physical methods (relaxation techniques promote muscle relaxation and reduction of anxiety, biofeedback, massage therapy, physical therapy,acupuncture, Transcutaneous electrical nerve stimulation (TENS);
- cognitive methods (distraction, such as singing or reading to the child, play activities, or imagining a pleasant place);
- hypnotherapy;
- prayer (the family's practice must be respected);
- other traditional practices that could be helpful and not harmful.

Children and family members should receive proper information about the mechanisms and appropriate treatment of pain, to help them better cope with the situation and increase better compliance. Health professionals should still remember that the methods described above are 'additionals', and should not be used in place of analgesic medications when they are necessary [4, 11, 13].

Pharmacologic treatment of pain

Considerations in treating infants and children. During the treating of pain in infants it is important to understand that although most of the major organ systems are anatomically well developed at birth, their functional maturity is often delayed. In the first months of life, in both preterm and full-term newborns, these systems rapidly mature, most approaching a functional level similar to adults before 3 months of age [46, 47].

The pharmacokinetics and pharmacodynamics of analgesics vary with age; drug responses in infants and young children differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems [46, 47, 48, 49, 50]. Tayman et al. [25] described that the clearance of analgesics may also be variable in young infants and children because development of renal function is incomplete: nephrons begin forming *in utero* at 9 weeks, formation is complete at 36 weeks, but functionally immature, GFR have a range of only ½ of adult values at birth, tubular secretion rate is only 20% of adult capacity. A less frequent dosing interval is needed to avoid accumulation and toxicity; however, poor renal elimination is more often the result of disease or hydration status. Age-

related differences in body composition and protein binding also exist. Newborns have a higher percentage of body weight as water and less as fat compared with older patients. Water soluble drugs, therefore, often have larger volumes of distribution [17, 18, 19]. Newborns, and especially premature infants, have diminished ventilatory responses to hypoxaemia and hypercapnia [18, 19] These ventilatory responses can be further impaired by CNS depressant drugs such as opioids and benzodiazepines [18, 19]. Except in the newborn period, when the half-life after administration is significantly longer, the pharmacodynamics and pharmacokinetics of nonsteroidal anti-inflammatory drugs (NSAIDs) in children are not much different than in adults [18, 19, 25]. However, the potential for gastrointestinal (GI), renal and other toxicities exist, but the incidence of these problems in young and older children may be less than that encountered during treatment of adults, perhaps due to the uncommon occurrence of the comorbidities and polypragmasia that predispose to problems [18, 19, 25].

Opioids are an essential element in pain management. There is no other class of medicines that is effective in the treatment of moderate and severe pain. The WHO supported the inclusion of morphine in the *WHO model list of essential medicines for children* to substantiate its use in children to relieve moderate to severe pain [50].

In the newborn's age, the elimination half-life of morphine is more than twice as long as that in older children and adults, as a result of delayed clearance [12]. Annand et al. [51] suggest that this appears to be due to several factors, the most important of which is the immaturity of the newborn infant's hepatic enzyme systems. Clearance of morphine is dependent on conjugation of the drug to form the metabolites morphine-3-glucuronide and morphine-6-glucuronide and the latter contributes a substantial fraction of morphine's analgesic effects. Tayman et al. [25] emphasized the role of glomerular filtration, which is reduced in the first week of life and leads to slower elimination of morphine's active metabolites.

These pharmacokinetic differences between neonates and older children must be understood to adjust dosing appropriately and avoid toxicity. Equally important in determining safe opioid dosing in infants is an understanding of the immaturity of the central respiratory control mechanisms [40, 50, 52, 53]. Infants in the first 3 – 6 months of life have inadequate and sometime paradoxical ventilatory responses to both hypoxia and hypercapnia, which can cause the development of apnea, or periodic breathing, after receiving even small doses of opioids [18, 19, 25].

Cardiorespiratory monitoring and careful observation is recommended whenever opioids are administered to infants less than 2 – 3 months of age. Premature infants and former premature infants with chronic lung disease continue to show depressed hypoxic drive for several months, and often require careful monitoring after opioid administration up to 5 – 6 months of age. Optimal use of opioids requires proactive and anticipatory management of side effects [50, 53, 54, 55].

WHO recommendations. Current WHO recommendations for the correct use of analgesic medicines in children relies on the following key concepts [43, 50]:

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

The WHO 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; for children assessed as being in moderate to severe pain, the administration of an opioid should be considered.

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 [43, 50].

Table 1 shows on-opioid analgesics for the relief of pain in neonates, infants and children recommended by WHO [43, 50]. According to WHO recommendations, 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 [43, 50]. 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 judgment, 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 [43, 50]. The feasibility of employing different routes of administration depends on the setting.

Table 1. Opioid analgesics for the relief of pain in neonates, infants and children recommended by WHO [43]

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

a Children who are malnourished or in a poor nutritional state are more likely to be susceptible to toxicity at
standard dose regimens due to reduced natural detoxifying glutathione enzyme.
b Maximum of 1 gram at a time.

Opioid analgesics. The use of strong opioid analgesics is recommended by the WHO for the relief of moderate to severe persisting pain in children with medical illnesses [50]. The opioid dose that effectively relieves pain varies widely between children, and in the same child at different times, and therefore should 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 [50]. An alternative opioid should be tried if

patients experience unacceptable side-effects such as nausea, vomiting, sedation and confusion [3, 50, 51, 52, 53]. The most common, troubling but treatable side-effect is constipation. Constipation also remains a problem with long-term opioid administration. A peripherally acting opiate μ receptor antagonist, methylnaltrexone, promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. The side-effect of nausea typically subsides with long-term dosing, but it may require treatment with anti-emetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist, such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia (PCA) with opioids may be effectively managed by a low-dose IV naloxone [53, 54, 55].

There is no upper dosage limit for opioid analgesics because there is no 'ceiling' analgesic effect. The appropriate dose is the dose that produces pain relief for the individual child. The goal of titration to pain relief is to select a dose that prevents the child from experiencing pain between two doses using the lowest effective dose.

The starting dose of opioids according to the WHO recommendations is shown in Tables 2, 3, 4, 5 [43, 50].

Table 2. Recommended by WHO starting dosages for opioid analgesics for opioid-naive neonates [43]

Medicine	Route od Adminis-tration	Starting dose
Morphine	IV injection[a]	25–50 mcg/kg every 6 hours
	SC injection	
	IV infusion	Initial IV dose[a] a 25–50 mcg/kg, then 5–10 mcg/kg/hour 100 mcg/kg every 6 or 4 hours
Fentanyl[b]	IV injection	1–2 mcg/kg every 2–4 hours
	IV infusion	Initial IV dose[c] 1–2 mcg/kg, then 0.5–1 mcg/kg/hour

[a] Administer IV morphine slowly over at least 5 minutes.
[b] The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.
[c] Administer IV fentanyl slowly over 3–5 minutes

Table 3. Starting dosages for opioid analgesics in opioid-naive infants (1 month – 1 year) according WHO recommendations [43]

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

[a] Administer IV morphine slowly over at least 5 minutes.
[b] The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.
[c] Administer IV fentanylslowly over 3–5 minutes.

Table 4. Starting dosages for opioid analgesics in opioid-naive children (1–12 years) according to WHO recommendations [43]

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

[a] Administer IV morphine slowly over at least 5 minutes.
[b] Administer IV fentanylslowly over 3–5 minutes.
[c] Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Useextreme caution when converting from one route to another. In converting from parenteral hydromorphone to oralhydromorphone, doses may need to be titrated up to 5 timesthe IV dose.
[d] Administer IV hydromorphone slowly over 2–3 minutes.
[e] Due to the complex nature and wide inter-individual variation in the pharmacokinetics of methadone, methadoneshould only be commenced by practitioners experienced with its use.
[f] Methadone should initially be titrated like otherstrong 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 increasesshould be performed at intervals of one week or over and with a maximum increaseof 50%.
[g] Administer IV methadone slowly over 3–5 minutes.

Table 5. Approximate dose ratios for switching between parenteral and oral dosage forms [43]

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

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

WHO guidance after a starting dose – the dosage should be adjusted on an individual basis to the level at which it is effective (with no maximum dose, unless further increase is not possible, because of untreatable side-effects) [43, 50]. The maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% while monitoring the patient carefully [43, 50]. Morphine is recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses.

There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.

Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability, including patient-related factors. Switching opioids and/or route of administration in children is strongly recommended in the presence of inadequate analgesic effect with intolerable side-effects. Alternative opioids and/or dosage forms as an alternative to oral morphine should, if possible, be available to practitioners, in addition to morphine. Routine rotation of opioids is not recommended [43, 50].

Continuous IV infusion of opioids is one effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing, without the pain associated with intramuscular injection [30]. The most common approach in paediatric centres is to administer a low-dose basal opioid infusion, while permitting patients to use a patient-controlled analgesia (PCA) device to titrate the dosage above the infusion. Using this method, dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; psychologically, the patient is more in control, actively coping with the pain, overall opioid consumption is lower, fewer side- effects occur, and patient satisfaction is generally much higher. Children as young as 5–6 years can effectively use PCA [53, 54, 55].

Children who have chronic pain related to cancer or other serious illness can be treated with long-term opioid therapy, typically with oral or transdermal delivery. The guidelines to optimize outcomes mirror those for adults [53, 54, 55].

If opioid analgesics are suddenly withdrawn, children display neurological signs, such as irritability, anxiety, insomnia, agitation, increased muscle tone, and abnormal tremors, and experience gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, diarrhea and poor appetite. In children, other withdrawal syndrome symptoms can also be observed, such as tachypnea, tachycardia, fever, sweating and hypertension [43, 49, 50, 51]. In children who have received significant doses of opioid analgesics for a long time there is an increased risk for the development of withdrawal syndrome. 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, and gradually increasing the time interval. In the case of a long-term therapy protocol, the dose should be reduced not more than 10–20% per week [43, 50]. These pharmacological approaches should be accompanied by measurement of withdrawal symptoms using a special scoring system [43, 50].

CONCLUSIONS

Children of all ages should receive effective pain treatment. Analgesics should be used in effective doses, and should not be limited to medical therapies alone. Healthcare practitioners should recognize that pain treatment and prevention is essential even when children are too young or cognitively unable to report the extent and severity of their pain.

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