A. Introduction

The majority of children with cancer worldwide experience medium to severe somatic, visceral, neuropathic, and/or spiritual pain. These distressing symptoms may be disease-related or treatment- (including procedure/intervention) related. Data reveals a significant under-treatment of pain in children with cancer both in the developed world and in developing countries.

However, children and parents expect pain to be relieved and parents may experience distress if they feel they are failing to protect their child from pain. The younger children are, the less likely it is that they receive appropriate analgesia. This chapter will describe treatment strategies in the management of acute cancer pain, as well as the management of procedural pain.

Data suggest that applying the World Health Organization (WHO) principles of pain management results in good pain relief for the majority of children with advanced cancer. State of the art pain management in the 21st century requires that pharmacological management be combined with
integrative, non-pharmacological therapies to manage a child’s cancer pain effectively.

B. Broad-band Analgesia

In the management of pain in children with advanced cancer, it may be necessary to combine non-opioids, opioids, integrative therapies, adjuvant analgesia, and rehabilitative and anesthetic or neurosurgical interventions. (B. Figure 1).

B. Figure 1
C. Pain Assessment

The majority of children with cancer suffer from pain, commonly as a result of disease-directed treatment (e.g., mucositis) or procedures (e.g., blood draws or bone marrow aspiration). In her landmark paper, Wolfe et al. documented the presence of pain in a large percentage of children with cancer towards the end of life, with approximately 70% of those patients experiencing distress and suffering as a result of pain. While most of the patients were receiving treatment to ameliorate the pain, fewer than half of the children had their pain symptoms adequately relieved by the treatment. Attention to pain and its management are essential to good medical care and a central component of palliative care.

Regular pain assessment, followed by appropriate analgesia is necessary to adequately relieve a child’s pain and suffering. Using one-dimensional self-report measures (e.g., visual analogue scales [VAS] or numerical rating scale [NRS] (with the anchor points 0 = no pain, 10 = worst possible pain) or faces scales, C. Table 1) provides easy pain assessment of alert and responsive children communicating with the caregiver or provider.

C. Table 1

Usual Starting Doses for patient (or nurse)-controlled analgesia (PCA) pumps - dose escalation usually in 50% increments both for continuous and PCA bolus dose (Pain Medicine & Palliative Care, Children's Hospitals and Clinics of Minnesota, USA). Doses for children > 6 months of age and are capped at 50 kg body weight.

<table>
<thead>
<tr>
<th></th>
<th>Continuous Infusion [mcg/kg/hour]</th>
<th>PCA bolus [mcg]</th>
<th>Lock-out time [minutes]</th>
<th>Maximum number of boluses/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 (max. 1000)</td>
<td>20 (max. 1000)</td>
<td>5-10</td>
<td>4-6</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3-5 (max. 250)</td>
<td>3-5 (max. 250)</td>
<td>5-10</td>
<td>4-6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1 (max. 50)</td>
<td>1 (max. 50)</td>
<td>5</td>
<td>4-6</td>
</tr>
</tbody>
</table>
For infants and children younger than 4 years of age, several validated pain assessment tools have been developed that require independent observers recording the physical behaviors, as well as the frequency of their occurrence. Several other well-validated tools, including COMFORT, CRIES, FLACC, and NIPS, can also be used, and comprehensive reviews comparing these assessment tools have been published.\textsuperscript{3-9} Behavioral observation measures to assess pain in cognitively impaired children are increasingly used.\textsuperscript{10-13}

Because children may suffer from different types of pain, such as somatic, neuropathic, visceral, or spiritual, to name a few, a single pain rating may not be sufficient to assess all dimensions of pain. A provider may have to become creative and more detail-focused to evaluate the different aspects of pain that a child experiences.

An example of detail-focused evaluation might include asking questions such as “Where have you felt pain today or where did you feel pain yesterday?” Having more background information might lead to questions such as “How would you rate the constant achy pain in your back, and how would you rate the occasional shooting pain in your leg,” or “Do you have pain anywhere else, in your heart or soul?”

C. References


**D. Integrative Pain Management**

State-of-the-art pain management in the 21st century demands that pharmacological management no longer be the sole approach to the management of a child’s pain and suffering. Integrative therapies, including cognitive behavioral techniques (such as guided imagery, hypnosis, abdominal breathing, and distraction) and physical methods (such as cuddle/hug, massage, transcutaneous electrical nerve stimulation (TENS), comfort positioning, heat, cold, and aromatherapy) may be utilized alone or together with pharmacology, Children cope better with pain and other distressing symptoms when they understand what is happening and when they are encouraged fully in the process to attain relief from their pain. Comprehensive pain control for children with advanced cancer requires tailoring to the needs of the individual child and integrating methods of pain management.
D. References


E. Pharmacological Pain Management

E.1 WHO-Principles

Data suggest that applying the 1998 World Health Organization (WHO) principles of pain management\(^1\) results in good pain relief for the majority of children with advanced cancer. These principles have recently been updated and replaced by the 2012 “WHO Guidelines on the pharmacological treatment of persisting pain in children with medical illness.”\(^2\) The WHO guidelines exclude acute traumas, perioperative pain, procedural pain, and chronic complex pain.

The following four pharmacological principles need to be applied to achieve good analgesia with cancer (or other persistent pain specific to situations with tissue damage where there is a clear role for pharmacological treatment):

- Using a two-step strategy (“by the analgesic ladder”)
- Dosing at regular intervals (“by the clock”)
- Using the appropriate route of administration (“by the appropriate route”)
- Adapting treatment to the individual child (“with the child”)
E.1.1 WHO-Principle #1: Using a Two-step Strategy “by the analgesic ladder”

**Step1: Mild pain.** Paracetamol (acetaminophen) and ibuprofen are the medicines of choice in the first step (mild pain). No other non-steroidal anti-inflammatory drug (NSAID) has been sufficiently studied in pediatrics 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 (acetaminophen) 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 (acetaminophen) 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 (acetaminophen).²

- **Paracetamol (acetaminophen):** (10–15 mg/kg PO/PR/IV q 4–6 hours; dose limit: <2 years: 40 mg/kg/day, >2 years: 75 mg/kg/day) is generally well tolerated by children and lacks gastrointestinal and hematological side effects. Significant hepatotoxicity²⁵ is rare, but careful attention to dosing is paramount. Although FDA-approved in the United States, there is not sufficient pediatric efficacy and safety data for the intravenous form of administration.

- **Ibuprofen:** (5–10 mg/kg PO q 6 hours; dose limit 2400 mg/day) has the least gastrointestinal side effects among the NSAIDs. It should be used with caution with hepatic or renal impairment and history of GI bleeding or ulcers and it inhibits platelet aggregation.
• **Ketorolac**: has the advantage of i.v. administration, but should be rotated to oral ibuprofen, as soon as tolerated (< 2 years: 0.25 mg/kg q 6 hours; > 2 years: 0.5 mg/kg 6 hours; max. 30 mg/dose; recommended dosing no longer than 3–5 days).

• **Celecoxib**: (a COX-2 inhibitor) might be considered if classical NSAIDs are contraindicated, e.g., due to bleeding risk, or gastrointestinal side effects. It does not display less renal toxicity compared to classic NSAIDs. Safety and efficacy has been established only in children 2 years of age or older and for a maximum of 6 months of treatment in juvenile rheumatoid arthritis (JRA) (1–2 mg/dose; max. 100 mg q 12–24 hours).

**E.1.2 WHO Principle #2: Dosing at Regular Intervals “by the clock”**

**Principle**: When pain is constantly present, analgesics should be administered, while monitoring side effects, at regular intervals (“by the clock” and NOT as an “as needed” basis).

Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing. “PRN only” may take several hours and higher opioid doses to relieve pain and results in a cycle of under medication and pain, alternating with periods of over medication and medication toxicity.

• **PRN only**: might be appropriate if pain episodes are truly intermittent and unpredictable. However, “PRN only” (without scheduled dosing) may unfortunately translate into “patient receives nothing” or “give as little as possible.” Pain in children is systematically under-treated—69% of
hospitalized pediatric patients for whom analgesics had been ordered did not receive a single dose in one study.\(^5\)

Commonly used opioid drug regimens include immediate release oral morphine every 4 hour or controlled-release morphine twice daily plus (for both strategies) a PRN dose of 10% of the 24-hour morphine requirement as an hourly immediate-release breakthrough pain medication as needed. (E. Table 1)

**E. Table 1**

Opioid analgesics: usual starting doses. Doses for children > 6 months of age and are capped at 50 kg body weight.

<table>
<thead>
<tr>
<th>Drug (Route of administration)</th>
<th>Equianalgesic dose (parenteral)</th>
<th>Starting dose IV</th>
<th>IV:PO ratio</th>
<th>Starting dose PO (transdermal)</th>
<th>Starting dose controlled release</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine (PO, SL, IV, SC, PR)</strong></td>
<td>10 mg</td>
<td>Bolus dose: 50-100 mcg/kg every 2-4 h Continuous Infusion: 10-30 mcg/kg/h</td>
<td>1:3</td>
<td>0.15-0.3 mg/kg every 4 h</td>
<td>0.45-0.9 mg every 12 hours</td>
</tr>
<tr>
<td><strong>Fentanyl (IV, SC, SL, transdermal, buccal)</strong></td>
<td>100-250 mcg</td>
<td>Bolus dose: 1-3 mcg/kg (slowly over 3-5 minutes · fast bolus may cause thorax rigidity) Continuous Infusion: 1-2 mcg/kg/h</td>
<td>1:1 (IV to Transdermal)</td>
<td>12 mcg/h patch (must be on the equivalent of at least 30 mg oral morphine/24 hours, before switched to patch)</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Hydromorphone (PO, SL, IV, SC, PR)</strong></td>
<td>1.5 mg</td>
<td>Bolus dose: 15-20 mcg/kg every 4 h Continuous Infusion: 5 mcg/kg/h</td>
<td>1:5</td>
<td>60 mcg/kg every 3-4 h</td>
<td>180 mcg/kg every 12 hours</td>
</tr>
<tr>
<td><strong>Oxycodone (PO, SL, PR)</strong></td>
<td>5-10 mg</td>
<td>n/a</td>
<td>n/a</td>
<td>0.1-0.2 mg/kg every 4-6 h</td>
<td>0.3-0.9 mg/kg every 12 h</td>
</tr>
<tr>
<td><strong>Codeine (not recommended)</strong></td>
<td>120 mg</td>
<td>n/a</td>
<td>n/a</td>
<td>0.5-1 mg/kg every 3-4 h</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Tramadol (PO, PR)</strong></td>
<td>100 mg</td>
<td>IV not available in USA [Bolus dose: 1 mg/kg every 3-4 h Continuous Infusion: 0.25 mg/kg/h]</td>
<td>1:1</td>
<td>1-2 mg/kg every 3-4 h, max. of 8 mg/kg/day (&gt;50 kg: max. of 400 mg/day)</td>
<td>2-4 mg/kg every 12 hours</td>
</tr>
</tbody>
</table>
Calculated rescue (breakthrough) dose: 10-16% of 24-hour opioid dose to be given every 1-2 hours as needed.

IV = intravenous, PO = by mouth, SL = sublingual, SC = subcutaneous, PR = rectal, n/a = not applicable

E.1.3. WHO-Principle #3: Using the Appropriate Route of Administration “by the appropriate route”

**Principle:** *Medications should be administered to children by the simplest, most effective and least painful route, making oral formulations the most convenient and least expensive route of administration.*

If possible, the route of administration should be chosen by the child. Painful intramuscular (IM) administration of pain medication is unnecessary and obsolete. Novel routes usually make use of high lipophilicity of certain opioids to cross skin or mucosa. The oral route (or enterally via nasogastric-tube/PEG-tube) is convenient, non-invasive, and usually preferred by pediatric patients and their care providers.

The titration of opioids by enteral route can occasionally be challenging due to the delayed onset of action compared to the intravenous route, which has a rapid and predictable onset of analgesia. Absorption efficiency and kinetics are variable and are influenced by the type of diet consumed by the patient, delayed gastric emptying, and first-pass metabolism.

The sublingual or buccal application of opioids (morphine, fentanyl, oxycodone, hydromorphone, and methadone) as well as intra-nasal administration of fentanyl are safe and are well-liked by children and caregivers. In fact, this is the preferred route of pediatric opioid application in our experience, if oral administration is not feasible and there is no intravenous access.

The data for the absorption and bioavailability of sublingual opioid shows a range, with morphine suggesting a bioavailability between 9% and 61%.

Although morphine has hydrophilic properties (and is therefore not ideal for the
sublingual route), the bioavailability of sublingual and orally administered morphine is, interestingly, not statistically different.\textsuperscript{6,7} Oxycodone has a sublingual bioavailability of less than 20\% and hydromorphone of 25\%.\textsuperscript{8} Methadone shows a good bioavailability via sublingual administration and very rapid onset of relief of breakthrough pain in seven adult patients in a dose of 2–8 mg.\textsuperscript{5,9} Case reports suggest good analgesia with sublingual liquid fentanyl,\textsuperscript{10} and a commercial sublingual fentanyl application is available, demonstrating a bioavailability of 65\%.\textsuperscript{11,12}

Clinically, we recommend using the oral starting doses of morphine and other opioids when utilizing the sublingual route and titrate to effect. The volume needs to be low (e.g., using for older children high-concentration compounds such as 20 mg morphine in 1 mL or 20 mg oxycodone in 1 mL—both are commercially available.)

- **Oral transmucosal fentanyl**: the fentanyl lozenge is a solid drug matrix with berry flavor providing oral transmucosal fentanyl citrate (OTFC). Due to fentanyl’s high lipophilicity, absorption across the oral mucosa directly into the systemic blood is rapid. OTFC has been used for children 3 years of age and above. Studies in opioid-naïve children showed typical opioid side effects of OTFC, including respiratory depression. Earlier pediatric trials, which reported higher rates of respiratory depression, either used high doses of OTFC (>20 mg/kg) and/or treated cardiosurgical patients, including children with cyanotic heart defects.\textsuperscript{13} Some pediatric trials reported nausea and vomiting commonly, others rarely or not at all. Due to these adverse effects, the indications for OTFC have been changed. Currently, OTFC is indicated exclusively for the treatment of breakthrough pain in cancer patients and is no longer used for sedation or pre-medication. If used for this purpose, certain guidelines\textsuperscript{14} should be followed. Intranasal application of opioids is pain-free and appears to be
Fentanyl can be diluted in normal saline solution (0.9%) and may be applied as a nasal spray utilizing a mucosal atomization device (MAD). The pharmacokinetic profile of intranasal fentanyl is similar to intravenous fentanyl. Intranasal fentanyl does not irritate the nasal mucous membrane and has only minimal ciliotoxic properties. Reported intranasal fentanyl doses in children (1–1.5 mcg/kg) are equal to or only slightly above suggested intravenous doses.

- **Transdermal fentanyl**: patches are contraindicated for acute pain management due to a long onset time (it may take more than 60 hours to reach peak concentrations in children), inability to rapidly titrate drug delivery, and long elimination half-life (up to 24 hours). Patches can be applied on intact, healthy skin every 48–72 hours. They must not be used for opioid-naïve children: patients need to be on the equivalent of 30–60 mg oral morphine/24 hours to safely rotate to a fentanyl patch. The smallest patch delivers 12 mcg/h. Sufficient immediate release breakthrough (rescue) opioid should be provided. Transdermal fentanyl has its role in stable pain, when children require opioids for more than a week.

- **Rectal application** (PR): may be unpopular and may deliver a wide variability in therapeutic blood levels through variable absorption. However, experience shows adequate analgesia might be achieved in children when suppositories (or liquid opioids via a small catheter rectally) are administered. In the US, suppositories are available for hydromorphone (3 mg), oxymorphone (5 mg), and morphine (5 mg, 10 mg, 20 mg, and 30 mg).
Adult data show that controlled (extended/sustained) release morphine tablets may be administered PR, at an oral:rectal conversion rate of 1:1.\textsuperscript{3,23}

- **Intravenous administration:** intravenous administration of opioids may be feasible, especially when there is a central line in place. Opioids administered intravenously will typically have an onset of action within 4–6 minutes (faster for fentanyl) and are relatively easy to titrate (with the exception of intravenous methadone). Titration of strong opioids by parenteral administration permits the adjustment of the medication to meet the patient’s needs and minimizes the potential for toxicity by allowing the patient to regulate the administration; patient (or nurse-) controlled-analgesia (PCA) pumps with a continuous background infusion as gold-standard as well as an as-needed bolus often provides excellent pain management.\textsuperscript{24} Opioids in pediatric PCA pumps include morphine, fentanyl, hydromorphone, and occasionally, methadone.

  Alternatively, opioid analgesics may be applied subcutaneously in the same dose as i.v., once high concentration/low volume (less than 1–2 mL/h) is ensured. In our experience, in palliative care, most children and their parents were comfortable with an i.v. (or occasionally s.c) PCA pump providing opioids for the management of pain and/or dyspnea in the home setting.

**E.1.4. WHO-Principle #4: Adapting Treatment to the Individual child - “with the child”**

**Principle:** *The treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis.*\textsuperscript{2}

The analgesic treatment should be individualized according to the child’s pain, response to treatment and frequently reassessed and modified as
required. Opioid dose titration is usually performed in 50% increment steps of the current dose (though not the starting dose), if it is not used in conjunction with sedation. These increments obviously might be higher or lower in individual cases.

In opioid dosing, “only the sky is the limit,” i.e., if there are no dose-limiting side effects such as over sedation or respiratory depression, the opioid should be titrated to effect and increased accordingly. As a result, some children may require extremely high doses of opioids (sometimes more than 100 times the starting dose) to control severe acute pain (usually in children with advanced cancer). Adjuvant analgesia (e.g., low-dose tricyclic antidepressants, gabapentinoids, low-dose ketamine, and benzodiazepines) may be appropriate in the pain management of the individual child, usually in addition to opioids.

With analgesic dosing, we would not expect over sedation. Patients and their parents do not have to choose between an awake and responsive child in pain and an over-sedated child. Nearly always, it is possible to provide good to excellent analgesia without over sedation. Response to the analgesic treatment must frequently be assessed using pain scales (see above) and assessing opioid-induced side effects (sedation, pruritus, nausea, etc.).

E.2 Non-Opioids

The most frequently used non-opioids are paracetamol (acetaminophen) and ibuprofen (alternative via intravenous administration: ketorolac).

- **Paracetamol (acetaminophen):** (10–15 mg/kg PO/PR q 4–6 hours; dose limit: <2 years: 60 mg/kg/d, >2 years: 90 mg/kg/d) is generally well tolerated by children and lacks gastrointestinal and hematological side effects. Significant hepatotoxicity\(^\text{15}\) is rare, but careful attention to dosing is paramount.
• **Ibuprofen:** (10 mg/kg PO TDS-QID; dose limit 2400 mg/d) has the least gastrointestinal side effects among the NSAIDs. It should be used with caution with hepatic or renal impairment and history of GI bleeding or ulcers and it may inhibit platelet aggregation.

• **Ketorolac** has the advantage of i.v. administration, but should be rotated to oral ibuprofen, as soon as tolerated (< 2 years = 0.25 mg/kg TID; > 2 years: 0.5 mg/kg q 6 hours; max. 30 mg/dose; recommended dosing no longer than 5 days).

**E.3 Weak Opioids**

As mentioned above, in 2012, the WHO recommendations changed from a three-step pain ladder (the now obsolete middle step was “weak opioids such as codeine”) to a two-step strategy for the treatment of persisting pain in children with medical illness. The new WHO guidelines however are explicitly excluding acute traumas, perioperative pain, procedural pain, as well as chronic complex pain. In certain circumstances however, especially in acute traumas or perioperative pain, in our experience, the weak opioid tramadol may play a role. Codeine and tramadol are so called “weak opioids” due to their ceiling effect (increasing above recommended dosing does increase adverse effects but does not increase analgesia).

Codeine can no longer be recommended for be recommended in pediatric analgesia. Codeine is a weaker analgesic than is commonly believed. A standard dose of many NSAIDs produces more effective analgesia than 60 mg of codeine in adults after surgery. Evidence has shown that the number needed to treat (NNT) is 16. In other words 16 patients have to receive 60 mg codeine postoperatively to improve 1 patient’s analgesia by 50%. Therefore, codeine is one of the weakest of all available analgesic drugs. The clinical experience that
codeine has a higher incidence of causing nausea and vomiting than most other analgesics used in children is backed by some evidence \(^{29}\) and non-significant trends.\(^{30,31}\)

More importantly, codeine is not a reliable analgesic, as its analgesic effect is produced only through its main metabolite, morphine. This pathway depends on the activity of a liver enzyme cytochrome P450 (CYP) 2D6. However, a large percentage of children, estimated at one third, are so-called poor or intermediate metabolizers for CYP 2D6 and show no (poor metabolizer) or remarkably inefficient (intermediate metabolizers) hepatic conversion of codeine to morphine.\(^{32}\)

Approximately 5% of white Caucasians and 29% of individuals of North African descent who have multiple copies of the enzyme CYP 2D6 are rapid metabolizers who are able to metabolize unusually high doses of morphine. Unfortunately, children have died after the administration of codeine.\(^{33,34}\)

Opioids (other than codeine) that are not recommended in pediatrics include the following:

- **Pethidine (meperidine) (e.g., Demerol®):** this opioid is metabolized into the neurotoxic metabolite normeperidine and should not be administered. Animal data show it to have a less constricting effect on the sphincter odi which can be advantageous in conditions such as cholecystitis or pancreatitis, though this has not yet been replicated in humans.

- **Nalbuphine (e.g., Nubaine®):** on its own functions as a weak opioid; however, since it is also a mu-receptor antagonist (like naloxone [Narcan®]), it may induce severe opioid withdrawal in an opioid-tolerant patient or block the efficacy of mu-antagonists, such as morphine, fentanyl, hydromorphone, methadone, or oxycodone.
• **Hydrocodone (e.g., Vicodin®, Lortab®):** like codeine, is metabolized by CYP 2D6 into hydromorphone (dilaudid®) with the same theoretical underlying issues of poor analgesia (poor-intermediate metabolizer) or over sedation (ultra-rapid metabolizer). Fatalities have been reported.\(^{35}\)

• **Combination Analgesia:** fixed combination analgesia, usually paracetamol (acetaminophen) plus an opioid, cannot be recommended in pediatric analgesia. Examples include paracetamol (acetaminophen)/hydrocodone (e.g., vicodine™), Paracetamol (acetaminophen)/oxycodone (e.g., percocet™, roxicet™) or Paracetamol (acetaminophen)/codeine (e.g., tylenol No3™). The fixed ratio of paracetamol (acetaminophen) to the opioid leaves unfavorable or dangerous choices. Using either suboptimal opioid doses or, when using adequate opioid doses, administering a liver-toxic dose of paracetamol (acetaminophen).

    Also, it is unclear what should be chosen for a rescue (breakthrough) dose of analgesia if a child receives a scheduled combination formulation. Providers cannot be certain that caregivers will administer additional doses of the drug, if their child remains in pain, thereby grossly increasing the risk of a paracetamol (acetaminophen) overdose. Due to the liver toxic ceiling effect of paracetamol (acetaminophen), it is usually not possible to increase/titrate the opioid to effect. In addition, parents may not be aware of other paracetamol (acetaminophen)-containing medications administered to their child. State-of-the-art pediatric analgesia, therefore, requires the individual titration of stand-alone paracetamol (acetaminophen) with a single opioid—the latter titrated to effect.
**Propoxyphen (Darvocet®):** Although not an opioid, should be mentioned here. It had been taken off the US market in 2011 by the FDA due to poor efficacy and significant (including cardiotoxic) side effects; however, some generic formulations may still be available.

### E.4 Strong Opioids

Opioids can be categorized into separate families: phenanthrene derivatives (morphine, hydromorphone, oxycodone, and hydrocodone), phenylpiperidine derivatives (fentanyl and meperidine), and diphenylheptane derivatives (methadone and propoxyphene).

An opioid rotation may be necessary, if dose-limiting opioid toxicity occurs. In our experience, this is necessary in about 10% of the children provided with opioids by the Pain & Palliative Care Team at the Children’s Hospitals and Clinics of Minnesota in Minneapolis St. Paul. An observation is that a switch from one opioid to another is often accompanied by a change in the balance between analgesia and side effects.

A favorable change in opioid analgesia to side-effect profile will occur if there is less cross-tolerance at the opioid receptors mediating analgesia than at those mediating adverse effects. If changing between opioids with short duration of action, start a new opioid (because of incomplete cross-tolerance) at 50% of equianalgesic dose and titrate to effect. Ceasing regular opioid analgesic drugs may provoke unpleasant withdrawal, even though a child may become unconscious during the last days of life due to the underlying disease (and not as an opioid toxicity).

- **Morphine:** morphine remains the most frequently used opioid and gold standard in pediatrics for treating moderate to severe pain. Opioid-associated side effects (e.g., constipation, pruritus, and nausea) need to
be expected and treated accordingly. For recommended starting doses, see E. Table 1.

Morphine undergoes a strong first-pass metabolism (with an oral:intravenous conversion of 3:1), and is metabolized by liver glucuronyl transferase into morphine-6 glucuronide (M6G) and morphine-3 glucuronide (M3G). M6G is a much stronger analgesic (times 40–100) and displays adverse effects including nausea, vomiting, sedation, and respiratory depression. M3G is not an analgesic and rather a mu-antidote with unique adverse effects, especially hyperexcitability/neurotoxicity.

The ratio of M6G/M3G thereby defines its analgesia to adverse effect profile in individual children. Both metabolites need to be excreted by the kidney, and children in renal failure have a higher risk of unwanted side effects. Fentanyl or methadone, neither of which are excreted renally, are likely to be a better choice in this scenario.

Morphine is considered to be the gold standard for analgesia and its action is the standard to which all other opioids actions are compared. It was introduced to clinical practice over 200 years ago and is derived from a species of poppy. Methods of morphine administration include oral, sublingual, intravenous, intramuscular, subcutaneous, intrathecal, and epidural. It has also been shown to be effective topically in open wounds.39

In standard practice, morphine is most commonly administered via the oral or intravenous routes. The currently accepted oral-to-intravenous potency ratio for morphine is 1:3. The usual practice when converting oral morphine to i.v. morphine is to divide the oral dose by 3. [3 mg oral morphine = 1 mg i.v. morphine]. Morphine for oral administration is available as a concentrated solution, immediate release tablets, and sustained release tablets and sachets (some of these preparations are not available in the USA).
The usual starting dose in pediatrics (children older than 6 months) for opioid-naïve patients is 0.05–0.1 mg/kg i.v. or 0.15–0.3 mg/kg PO q 4 hours titrated to effect. The extended (or sustained) release form of morphine available in the United States only comes in tablets or capsules and smaller children will usually not swallow them. A common off-limit use is to open the capsule and administer the containing granules in yogurt or applesauce. The granules might also be administered through a G- or J-tube, however, the granules may clog smaller caliber tubes.

In some children, 12-hour extended release opioid may not last the full 12 hours and the children will display end-of-dose failure. An administration every 8 hours would be advisable in such cases. Extended-release opioid tablets/capsules cannot be crushed or dissolved in fluids, as that would release the opioid immediately, which poses the danger of opioid over-sedation.

Of note, in most countries outside the United States, extended-release morphine exist as “sachets,” i.e., a powder containing extended-release granules that can be easily dissolved in 10 mL of water; only a percentage of this preparation will be administered, making weaning or titration of extended-release opioids in pediatrics significantly easier.

- **Renal Impairment:** M3G is not analgesic, it is actually nociceptive and does not bind to opioid receptors; it may be responsible for some of the adverse CNS effects such as myoclonus. M3G and M6G are excreted by the kidney and their elimination is directly related to creatinine clearance. In renally compromised patients, M3G and M6G may accumulate in the blood and cerebrospinal fluid, leading to unwanted toxicity. In M6G this leads to over sedation, pruritus, nausea, etc.; in M3G, increased nociception and hyperexcitability. Caution should be used when administering morphine to patients with renal impairment.
• **Liver Impairment:** only in patients with severe liver failure, as indicated by, for example, increased prothrombin time, does morphine’s half-life increase, making possible opioid-induced side effects more likely.

• **Morphine in neonates:** morphine appears to be safe and efficacious in term neonates; however, starting doses are usually lower compared to those used in older children.

  o **Starting doses (titrated to effect):**
    
    PO/SL: 0.07–0.15 mg/kg q 4–6 hours
    
    IV/SC: 0.025–0.05 mg/kg q 4–6 hours
    
    Infusion: 7–10 mcg/kg/h plus
              7–10 mcg/kg clinician administered
    
    PCA bolus: 2–4 boluses/hour

  
  A study of long-term outcomes of preterm babies exposed to continuous morphine infusion displayed showed no adverse effect of morphine on intelligence, motor function, or behavior 5–6 years in a study.40 Opioid pharmacokinetics and pharmacodynamics in neonates and young infants (up to 6 months of life) require us to administer starting doses that are lower than the doses used in older children. This is based on the following:

  1. Infants display a delayed maturation of hepatic enzyme systems involved in drug metabolic inactivation, an infant’s metabolism has matured enough to enable the use of most opioid analgesics by the age of approximately 6 months.

  2. Decreased glomerular filtration and renal tubular secretion results in decreased elimination of opioids and their active metabolites.
3. Decreased levels of α1-acid glycoprotein and albumin translate into decreased plasma protein binding for many drugs and therefore results in increased concentrations of pharmacologically active unbound drug.

4. As a result of the above, morphine elimination half-life in children older than 6 months is 3–4 hours. In term infants, the half-life is 7 hours, and in preterm infants, 9–10 hours. (This explains why we might schedule morphine every 4 hours in a 1-year-old, but every 6–8 hours in a 1-day-old term infant.

5. Infants have immature ventilatory reflexes in response to hypoxia and hypercarbia and have an increased risk of hypoventilation in response to opioids and therefore need to be more closely observed than older children.

6. However, morphine does not provide adequate analgesia for acute procedural pain among preterm neonates, and for that reason, fentanyl might be a better opioid choice to manage acute pain in this age group (however, it may result in faster development of opioid tolerance). The liver of neonates and young infants (biliary excretion results in small intestine absorption) preferentially produces M3G, and hardly any M6G.

E.5 Other opioids commonly used in pediatric analgesia

- **Oxycodone**: oxycodone is a selective mu-opioid receptor agonist, although some animal studies suggest a kappa receptor agonist activity. The potency of oral oxycodone as compared to morphine is between 1:1 and 2:1. One advantage of oxycodone over morphine is the slightly
longer half-life, frequently allowing a q 6 hours dosing (as oppose to q 4 hours in morphine). Renal and hepatic impairment increases the oxycodone serum level.43

- **Hydromorphone**: hydromorphone is another selective mu-opioid receptor agonist. Unlike morphine metabolism, there is no hydromorphone-6-glucoronide (H6G), but similar to the morphine metabolism, there is hydromorphone-3-glucoronide (H3G). Opioid hyperexcitability has been reported in patients with renal failure taking hydromorphone.44,45 Normal H3G to hydromorphone plasma ratio is 27:1, but in renal failure, it is 100:1.46

- **Fentanyl**: this is a popular opioid for analgesia prior to painful procedures due to its rapid onset (about 1 min) and its brief duration of action (30–45 min). It is also used to manage the pain of children with cancer, for intra- and postoperative analgesia, in pediatric palliative care, and in sedation analgesia for ventilated children in the intensive care unit. Fentanyl provides a good alternative to morphine when dose-limiting side effects of the latter mandate a rotation of opioid drug.47,48,49

- **Methadone**: methadone is an excellent opioid choice in pediatric palliative care and remains underutilized. It is a mu (delta, kappa)-opioid receptor agonist, an NMDA-receptor antagonist, and a presynaptic blocker of serotonin and norepinephrine re-uptake.

  Advantages include methadone’s long half-life (allowing BID or TID dosing), high effectiveness in chronic pain relief as well as in the management of neuropathic pain, NMDA receptor antagonist mechanism (helps preventing tolerance), lower incidence of constipation, absent
active metabolites, safe usage in renal failure and in stable liver disease, and its low cost.

There are disadvantages to using methadone, including wide dosing variation, long half-life (may lead to accumulation; making quick titration difficult), and more complex equianalgesic conversion, which requires a much longer and closer patient observation than other opioids.

We use an equianalgesic conversion chart (E. Table 2) when switching to oral (or sublingual) methadone in our pediatric patients. When switching from the oral to intravenous route of administration (either TID, or continuous infusion via a PCA-pump with additional boluses), we use 50–80% of the oral daily methadone dose. Methadone should not be prescribed by those unfamiliar with its use. Its effects should be closely monitored for several days, particularly when it is first started and after any dose changes.

## E. Table 2

Usual starting doses for patient (or nurse)-controlled analgesia (PCA) pumps - dose escalation usually in 50% increments both for continuous and PCA bolus dose (Pain Medicine & Palliative Care, Children's Hospitals and Clinics of Minnesota, USA). Doses for children > 6 months of age and are capped at 50 kg body weight.

<table>
<thead>
<tr>
<th></th>
<th>Continuous Infusion [mcg/kg/hr]</th>
<th>PCA bolus [mcg]</th>
<th>Lock-out time [minutes]</th>
<th>Maximum number of boluses/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 (max. 1000)</td>
<td>20 (max. 1000)</td>
<td>5-10</td>
<td>4-6</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3-5 (max. 250)</td>
<td>3-5 (max. 250)</td>
<td>5-10</td>
<td>4-6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1 (max. 50)</td>
<td>1 (max. 50)</td>
<td>5</td>
<td>4-6</td>
</tr>
</tbody>
</table>

Opioids should not be administered to children with chronic pain, which is defined as pain that extends beyond the expected time of healing, including tension headaches/migraines, chronic musculoskeletal pain/fibromyalgia,
chronic sickle cell pain (pain that extends beyond the expected time of acute vaso-occlusive crisis, e.g., 5–10 days plus time to wean the opioid), and functional abdominal pain.

**E.6 Opioid Wean**

For both i.v. and enterally administered opioids, in our experience, might be decreased rapidly, (by 33% every 12–24 hour), carefully watching for opioid withdrawal (using the Withdrawal assessment Tool Version 1 [WAT-1] score) if opioids were administered for a shorter time than 3–5 days and underlying pain was improved by therapy or natural cause of disease. For opioids administered longer than 5–7 days, in our experience, a daily wean of 10% of the current dose will work for the majority of children.

The time to wean the opioid, however, should usually not be longer than the time the patient has been receiving opioids during his pain management. An opioid may be discontinued, after it has been administered at 50% of the (lower-end) starting dose for 24 hours without any signs of withdrawal.

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**E. References**


F. From Needle-pokes to Bone Marrow Aspiration: Procedural Pain Management in Children with Cancer

Children with malignant diseases often require many procedures of varying intensity over the course of their illness. A combination of approaches that includes adequate planning, appropriate medications, as well as behavioral and integrative strategies can engage the child’s cooperation, minimize resistance, and prevent the development of more painful experiences in the future.

In the 21st century, children and their parents must expect advanced treatment protocols for all procedural pain (such as blood draws, venous access, Port-a-Cath access, lumbar puncture, chest tube insertion, suturing, etc.) for all children with cancer. Unfortunately, even in resource-rich countries, not all children’s hospitals have implemented this approach.

The memory of previous painful experiences has a great influence on pain experiences during subsequent procedures. Early pain experiences influence later responses and it is important to provide excellent procedural analgesia the first time a child comes under care and/or into our institution; inadequate analgesia for initial procedures in young children (8 years or younger) diminishes the effect of adequate analgesia in subsequent procedures.
What are the essential components of a state-of-the-art procedural pain management protocol? As we will discuss, at a minimum, a procedural pain management protocol must include the following “non-negotiable” essential components:

- Positioning
- Distraction
- Topical anesthesia
- Sucrose (for 0–12 months of age)
- Possible addition of analgesia/sedation

If excellent analgesia cannot be achieved by the means mentioned above (or cannot be integrated in the current clinical setting), consider the addition of analgesia (intranasal fentanyl) and/or an appropriate level of sedation, depending on whether the procedure ranged from minimal sedation (e.g., nitrous gas) to moderate or even deep sedation (ketamine, propofol).

**F.1 Essential component #1: Positioning for Comfort**

- Appropriate for infants and toddlers (as well as for many—but clearly not all—older children)
- Will increase the child’s sense of support
- The child is less likely to resist the procedure

When a child is undergoing a procedure while awake, positioning and holding the child well are key to ensuring that the procedure goes well. A child that feels comforted and supported is more likely to be cooperative, while a child who feels held down is likely to resist. Positioning children for comfort helps the infant or young child feel secure and close to the parent while keeping them still and quiet for the procedure. For simple procedures, it is
often helpful to hold the infant or toddler in the parent’s lap, facing the parent. Swaddling has been shown to be effective if the infant needs to lie down. If the young child can sit in the parent’s lap for the procedure, the following holds work well:

- Having parent hold the child on his or her lap.
- One of the child’s arms embraces the parent’s back under the parent’s arm.
- The other arm is controlled by the parent’s arm and hand. Parents can control both arms of an infant with one hand.
- The child’s feet are held between the parent’s thighs, anchoring the child’s legs. The parent can also use his other arm to control the legs.
- The excellent recommendations for vaccination pain in children also hold true for most other painful procedures, such as a blood draw, venous access, finger or heel stick, etc. To reduce pain at the time of injection, do not place children in a supine position.³

As mentioned previously, whenever feasible, offer a choice of position to the child, including a caregiver’s lap. To review this concept, see an example from the Royal Children’s Hospital in Melbourne, Australia. This example demonstrates how parents can assist their children during a painful procedure. http://www.rch.org.au/comfortkids/resources.cfm?doc_id=10140

F.2 Essential component #2: Distraction

There is significant evidence demonstrating the positive effects of utilizing integrative therapies for painful procedures in children. In a Cochrane review⁴ of 28 trials with 1951 children aged 2–19 years undergoing needle-procedures (immunizations and injections), the following strategies proved to be effective:

- Distraction
- Hypnosis
• Combined cognitive-behavioral interventions

In addition, the following was promising but had more limited evidence:

• Information/preparation
• Nurse coaching plus distraction
• Parent positioning plus distraction
• Distraction plus suggestion

To reduce pain at the time of injection among children four years of age and older, offer to rub or stroke the skin near the injection site with moderate intensity before and during vaccination or other needle procedures (grade B recommendation, based on level II-1 evidence).6

Consider involving caregivers by offering parent coaching, either by offering educational information such as a brochure or through face-to-face communication. Certain types of parental behaviors (such as nonprocedural talk, suggestions on how to cope, and humor) have been reported to decreases in children’s distress and pain. However, other behaviors (such as reassurance or apologies) have been related to increases in children’s distress and pain.5

Distraction minimizes a child’s fear, anxiety, and pain. The mechanism by which distraction works is not fully understood but is likely a combination of diverting attention away from painful and distressing stimuli, focusing the brain, reducing the capacity for awareness of noxious stimuli, and engaging in a pleasurable activity that releases endorphins.

Children will vary in their desire to either watch a procedure or to look away. If a child wishes to watch and is forced to look away he may become more distressed. Many children will choose a distraction but periodically look back at the procedure in progress. It helps to have a staff member comment on how well it is going, provide praise to the child on his cooperation or to do a time check by informing the child how much time is left or by making comments such as “we are half-way done.”
In general, strategies that reinforce the child's capacity for self-control will contribute to more successful procedural experiences.

Many children, especially young children, can be distracted with stories or books read aloud, the more familiar the better. The storyteller or reader should engage the child by asking questions such as “What do you think will happen next,” or “what is this character’s name?” This is a good role for parents if they are comfortable being helpers. Other possible distractions are puppets, therapy animals, or blowing bubbles.

Older children and teens can be quite distracted by video games. A video game might serve as an excellent distraction during procedures such as wound debridement or dressing changes. Additionally, there are biofeedback programs that measure levels of relaxation, such as decreased muscle tension or lowered heart rate that can be used during procedures for which the child is awake. Examples include electrodes that measure muscle tension or finger sensors for pulse or temperature. Devices can be simple (skin thermometers) or complex (laptop computers). As the child focuses on breathing or relaxation, they can watch the device to see how it changes. This can reinforce the child’s sense of mastery and control.

F.3 Essential Component #3: Topical Anesthesia

Topical local anesthetics (e.g., topical lidocaine including EMLA, LMX, J-tib—), which effectively numb the skin, are the single most important interventions in our tool box and must always be offered in preparation for painful procedures. Obviously, children and especially teenagers may decline the offer, or in life-threatening events, we may forgo administration, but otherwise, every single needle procedure protocol must include the offer of a topical local anesthetic.

Topical anesthesia and local anesthetics are critically important to the overall effectiveness of managing procedural pain and reducing the child’s
anxiety. Large doses of the medications may have their own sedating effects and can enhance sedative effects when used in combination with other sedatives or opioids. These agents are cardiac depressants, so the maximum allowable safe dosage should be calculated before administration to avoid overdose. Again, evidence captured for vaccination procedures holds true for other needle procedures. To reduce pain at the time of injection, encourage parents to use topical anesthetics during needle procedures.

Topical anesthetics are considered safe for use in children of all ages. However, administration of excessive doses or prolonged application times can lead to serious adverse effects, including irregular heartbeat, seizures, and difficulty breathing.\textsuperscript{7} For children undergoing needle procedures, there is insufficient evidence for or against the use of skin-cooling techniques (vapocoolants, ice, and cool or cold packs) to reduce pain at the time of injection (grade I recommendation, based on conflicting level I evidence).

The choice of topical anesthetic depends on the clinical scenario. The most important step is to administer the topical local anesthetic before the needle procedure. The 3 most commonly administered topical creams are EMLA cream (lidocaine 2.5% and prilocaine 2.5%), ela-max LMX (4% lidocaine topical anesthetic cream), and ametop gel (4% amethocaine [tetracaine]). The choice of anesthetic may depend on application time (EMLA: 60 min, LMX: 30 min, J-Tip: immediately), on practicability (in the United States, LMX is available over-the-counter, whereas EMLA requires a prescription), and cost (J-tip is more expensive than EMLA or LMA).

**EMLA compared to Ela-Max LMX:**

- **Administration Time:** in comparison to EMLA, Ela-Max LMX and amethocaine gel only need to be administered for 30 minutes (versus 60
minutes for EMLA)\textsuperscript{8,9,10}

- **Analgesia duration after cream/patch removal:** EMLA 1–2 hours vs. LMX 1 hour

- **Skin time** (how long might the cream/patches be administered): EMLA 4 hours vs. LMX 2 hours

- **Efficacy:** All 3 creams work well; however, in a Cochrane review, Ametop gel (4% amethocaine [tetracaine]) marked slightly better. “Although EMLA is an effective topical anaesthetic for children, amethocaine is superior in preventing pain associated with needle procedures.”\textsuperscript{11}

**F.3.1 EMLA® in Neonates**

In neonates, EMLA reduces the behavioral pain response to venipuncture but not heel lance. Single doses in neonates have not been associated with methemoglobinemia and EMLA has been shown to be effective for lumbar puncture in neonates greater than 34 weeks gestation.\textsuperscript{12,13}

**F.3.2 Buffered subcutaneous Lidocaine**

Buffered (non-buffered lidocaine is painful during administration) intradermal and subcutaneous lidocaine has been shown to be as effective as Ela-Max LMX for preventing pain during i.v. insertion in children.\textsuperscript{14,15,16} However, it may occasionally be difficult explaining to a child that he or she needs several needle sticks to not feel the needle procedures: Having said this, pain from a 30-gauge needle stick may be barely noticeable, especially when distraction is used during the needle stick administration of the lidocaine.
F.3.3 Needleless Lidocaine Injectors

The J-tip is a single-use, disposable, carbon-dioxide-powered, needleless lidocaine injector. Despite its significant cost, this device has proven to be very popular among children and pediatric providers in situations where waiting for 30 min (using an Ela-Max LMX or amethocaine gel) is not to be feasible. Noise of activation might startle children and although the administration doesn’t hurt, there is usually a tiny drop of blood at the site where the lidocaine is injected, which may cause younger to children cry when they see it. If using this device for a needle procedure, the clinician has to be very precise in its use (only a 3-mm zone will be numb). The device can drive the lidocaine quite deep: on the back of a hand, not only might it numb the spot on the skin, but it might also cause a digital nerve block lasting nearly an hour.

F.4 Essential Component #4: Sucrose for Children 0–12 Months of Age

Administering sucrose is effective in managing mild-medium procedural pain in children 0–12 months of age. The administration reduces pain and crying during painful procedures, such as venipuncture. Endogenous opioids seem to play an important role, as the mu-opioid receptor antagonist naloxone blunts the analgesic effect.\textsuperscript{17} The effective dose of sucrose (24%) is 0.05–0.5 mL (= 0.012–0.12 g), administrated (e.g., with a pacifier) 2 minutes prior to mild to moderately painful procedures. The duration of analgesia is about 4 minutes.

F.5 Consider Additional Analgesia and Sedation

If the strategies such as positioning, integrative therapies and topical anesthesia cannot guarantee excellent procedural pain management in the
individual child or for the individual procedure, the next steps would be to consider either systemic opioids by different routes of administration including intranasal, sublingual, buccal, intravenous, and oral administration, or to consider using agents such nitrous gas, ketamine, or propofol, depending on the child and the procedure. There is data that supports the intranasal administration of fentanyl for procedural pain in children.\textsuperscript{18,19}

If positioning, integrative therapies, topical anesthesia, and systemic analgesics are not adequate to provide excellent analgesia for a certain procedure in an individual child, then the child must be sedated in a safe environment. Holding down a crying child to perform a painful procedure cannot be tolerated anymore in the 21\textsuperscript{st} century.

There are occasions that require sedation to safely manage procedures. These may be complex procedures or situations where the child’s ability to cope has seriously deteriorated. Sedation is also a helpful strategy to minimize the burden of painful procedures, like bone marrow aspiration, for example. There are different levels of sedation, and in general, using the lightest sedation to ensure comfort and achieve the necessary results is desired. When sedation is required for procedures, careful planning is important.

\textbf{F.6 Minimal Sedation}

Minimal sedation is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. Children who have received minimal sedation generally will not require more than observation and intermittent assessment of their level of sedation. Some children will become moderately sedated despite the intended level of minimal sedation:

- Drug-induced state during which patients respond normally to verbal commands
• Cognitive function and coordination may be impaired
• Ventilatory and cardiovascular functions are unaffected
• Generally does not require more than observation and intermittent assessment of their level of sedation

Nitrous gas is an excellent example of a safe agent successfully used worldwide as analgesia during painful procedures:
• Successful for a variety of painful procedures in children.
• The use of nitrous oxide for minimal sedation is defined as the administration of nitrous oxide to a level where a child is still responsive (usually 50–60%)
  – No other sedative, opioid, or other depressant drug
  – Healthy patient
• Patient is able to maintain verbal communication
• If combined with other sedating medications or used in concentrations more than 50%, the likelihood of moderate or deep sedation increases

Nitrous oxide in oxygen with varying concentrations has been successfully used for many years to provide analgesia for a variety of painful procedures in children. The use of nitrous oxide for minimal sedation is defined as the administration of nitrous oxide to a level where a child is still responsive (50–70% or less) with the balance as oxygen, without any other sedative, opioid, or other depressant drugs given before or concurrently with the nitrous oxide to an otherwise healthy patient in ASA class I or II. The patient is able to maintain verbal communication throughout the procedure.

If nitrous oxide in oxygen is combined with other sedating medications, such as benzodiazepines, or an opioid, or if nitrous oxide is used in concentrations of more than 50% (maximum: 70% nitrous gas; 30% oxygen), the likelihood for moderate sedation increases. In this situation, the clinician must
be prepared to institute the guidelines for moderate or deep sedation as indicated by the patient’s response.

F.7 Procedural Pain

1. Procedural pain must be avoided all the time. The means to avoid needless pain exist in any pediatric institution and our patients, their families, and our staff expects protocols to be put in place to help patients avoid needless pain.

2. If good analgesia is not feasible, utilize mild sedation (nitrous gas), moderate or deep sedation, or general anesthesia such as ketamine and propofol in a safe environment.

3. Marshaling attachment resources by enlisting a child’s favorite object or parent. Invite the child to hold on to his or her favorite toy or blanket, and have the parent in the room as long as the child is awake and responsive.

4. Always implement distraction and integrative therapies.

5. Offer choices and provide control to the child. One of the worst feelings a child can experience is to be completely, utterly out of control in the clinical environment. We have to strive to give as much control back to the child (within the limits of achieving our clinical goals) as possible. Examples of offering control to the child include the following:
   - “Johnny, would you like to have the EMLA patch on the left hand or the right hand?”
   - “Sarah, would you like to lie down or sit on daddy’s lap?”
• “Kathy, who should take the LMX patch off—mummy, me, or yourself?”

6. We need to watch our language.
   • We must not lie, using phrases such as “This is not going to hurt.”
   • We should avoid terms, such as “hurt,” “pain,” ”just like a bee sting,” etc.
   • Give children a job to help themselves: “Let’s work together to make sure that this injection doesn’t bother you. Okay, to do that, you have a job to do. Choose either bubble, or pinwheel (or this smart-phone “App” or video game) and blow (focus)—that’s it. Really blow (focus) because that way the needle doesn’t bother you…okay?”
   • Praise “good job,” “well done” during the procedure as the child is using his/her distraction techniques

7. Positioning is important
   • When a child is undergoing a procedure while awake, positioning and holding are key to the procedure going well. A child who feels comforted and supported is more likely to be cooperative, while a child who feels held down is likely to resist.

8. The majority of toddlers, children, and adolescents are “information seekers.” Age-appropriate explanations and demonstrations (such as playing the procedure on a teddy bear, etc.) are often extremely helpful.

9. Use distraction such as hypnosis, magic glove, imagery, breathing, and bubble blowing.
10. Harness the child’s imagination by using hypnotic suggestions to reduce the perception of pain. Invite the child to imagine the following:

- If you could be at any place right now, where would you be, what is there, how does it look? What are you doing, seeing wearing? "20
- “Magic glove” is an easy technique to learn. The technique involves teaching parents or clinicians to apply an imaginary “magic glove” on a hand numbing the skin with several gentle strokes, “until it is just right” for the child.
- Excellent 3-day courses in pediatric hypnosis in the United States are available from the National Pediatric Hypnosis Training Institute. [http://www.nphti.org/](http://www.nphti.org/)

11. Consider offering a bonus or present (treasure box). At the very second you begin the painful procedure, it may be helpful to make a comment to the child similar to the following script, “Did you know that all children who have done such a great job are going to get something out of our treasure box?” While the provider mentions the treasure box, have another person put the box, which may include items such as stickers, or small toys, within the child’s reach.

12. If possible, it is important to empower parents or caregivers by allowing them to be helpful during painful procedures. Under no circumstance is their job to hold the child down; instead, their role should be to provide comfort. A handout or discussion with parents and care providers before the procedure may be helpful. Children aged 5–10 years may perceive their parents worry even as parents attempt to provide reassurance, whereas distraction is associated with increased child coping."21
13. Local anesthesia (topical lidocaine, EMLA, LMX, J-tip, etc.) must always be a part of the procedural pain protocol if young children are not under deep sedation or general anesthesia or if they are not experiencing a life-threatening event. In particular, older teenagers may choose not to have topical anesthesia administered, and that choice should be honored.

14. The appropriate analgesia and anxiolytic must obviously be administered by a non-painful route. An example of this is the use of intranasal fentanyl.

15. The clinical staff needs to be organized and ready before the child is brought into the procedure room.

It is important to manage pain and comfort during procedures. Lack of pain management can lead to physiologic instability, increased pain experiences in future, and distressing behaviors. Management of procedural pain will have an impact on how the child relates to the healthcare team and responds to future procedures. A multi-modal approach that combines pharmacologic, behavioral, and integrative interventions together with parent and child preparation is most likely to result in a successful procedure.

F. References


G. Neuropathic Pain and Adjuvant Analgesia
Although pediatric data is limited, evidence from treatment of adult neuropathic pain supports the use of strong opioids, tricyclic antidepressants, and anticonvulsants. Opioids are first-line analgesia in pediatric neuropathic cancer pain, though they often must be combined with other adjuvant drugs.

**G.1 Tricyclic Antidepressants**

The mechanism of action in tricyclic antidepressants (TCAs) seems to be based on serotonine/noradrenaline re-uptake inhibition, which stimulates descending inhibiting pathways stemming from the periaqueductal grey. Adverse effects of all TCA include arrhythmia and anticholinergic/antihistamine effects, such as dry mouth, constipation, urinary retention, blurred vision, and sedation. Nortriptyline may be better tolerated than amitriptyline. Cases of the use of amitriptyline in pediatric cancer neuropathic pain have been reported, but there are no RCT data.

Doses above 25 mg/dose for teenagers for both amitriptyline and nortriptyline are rarely necessary. The TCA dose should be gradually reduced over 1–2 weeks to avoid unpleasant withdrawal effects. The sedating effect (to improve sleep initiation) may commence immediately; however, the analgesic effect may not become effective for days to weeks. There is anecdotal evidence of sudden death in children using desipramine.

**G.2 Gabapentinoids**

Gabapentin is widely used in pediatric neuropathic and chronic pain management, usually second-line in combination with a first-line TCA. Adverse effects occur usually if dose is started too high or escalated too fast, but even with slow dose escalation, side effects may occur. These include ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, and peripheral edema. When
gabapentin is weaned, the dose should be decreased gradually over 1–2 weeks. The analgesic effect may take days to weeks to occur.

If gabapentin fails once the maximum dose is reached, or because of dose limiting side effects, one may switch to pregabalin at a conversion rate of about 6:1 (i.e., 600 mg gabapentin equals 100 mg pregabalin). Data reveal that patients who fail to benefit from gabapentin may benefit from pregabalin and the other way around. No data exist to suggest that either drug is better than the other one.

G.3 Sodium-Channel Blocker

The local anesthetic lidocaine 5% patch is effective for diverse peripheral neuropathic pain conditions and allodynia. It may be used for localized pain only. The patch is a matrix and can be cut to fit. The drug maker recommends 12 hours on/12 hours off to avoid tolerance; however, a raised systemic lidocaine level is very unlikely even with extended usage.

G.4 NMDA-Receptor Antagonists

Ketamine is a dissociative anesthetic, which has analgesic properties in sub-anesthetic doses. Low-dose analgesic dose is in the range of 0.06–0.3 mg/kg/h i.v. The common adverse effects seen anesthetic usage (intracranial hypertension, tachycardia, and psychotomimetic phenomena such euphoria, dysphoria, and vivid hallucinations), usually do not occur at low-dose, but can be managed with a benzodiazepine. Data suggests that a short-term “burst” treatment with ketamine may have long-term benefits. Steady-state oral/parenteral ratio is unclear, but estimated at about 3:1 (i.e., the oral dose is up to three times as high as the intravenous one). The i.v.-formulation of ketamine has a bitter taste, and when administered orally should be mixed with
a flavor. There is anecdotal evidence, that the concurrent administration of low-dose ketamine and methadone has improved effectiveness, hinting at a possible heterogeneity of the NMDA-receptors.

G.5 Other Adjuvant-Analgesia

- Corticosteroids by their anti-inflammatory actions. Due to potentially serious side effects, administration should be short term.
- Muscle relaxants, such as baclofen or cyclobenzaprine
- Low-dose benzodiazepines, such as diazepam, lorazepam, or midazolam
- Bisphosphonates (for bone pain due to metastatic cancer), such as pamidronate
- Antispasmodics, such as hyoscine butylbromide, hyoscyamine, oxybutynin, or glycopyrrolate

H. Barriers to Appropriate Opioid Use

Many myths still remain and may be responsible for the inadequate pain management of many children in cancer care. In particular, infants and very young children as well as severely impaired children and teens often do not receive sufficient analgesia, because their discomfort is different from that of adult. It is fallacious to believe that children’s nervous systems are immature and therefore unable to perceive experienced pain. All available data suggests that those theories are wrong. The application of an opioid to treat pain or dyspnea does not hasten a child’s death, if titrated by effect. The correct provision of opioids for symptom management not only improves the quality of life of a dying child significantly, but often prolongs the end-of-life period due
to the improved quality of life.

Clinicians might encounter prevailing myths, misconceptions, assumptions, and appropriate concerns about opioids, which may act as barriers to their appropriate use. These include (but are not limited to) the following:

- Opioids causing addiction (chemical dependence).
- Opioids causing over sedation/respiratory depression.
- Opioids causing ileus/gut hypomobility/constipation.
- Medication being “too strong.”
- Administering opioids near the end of life means “we are giving up” or “hastening death.”

H.1 Myth #1: Opioids lead to Addiction

Tolerance and withdrawal are physiological phenomenon not to be confused with dependence syndrome (“addiction”), which involves behavioral and cognitive phenomena, including a strong desire to take the psychoactive drug, persisting in its use despite harmful consequences, and giving a higher priority to drug use than to other activities and obligations.² There are no published data to suggest that appropriate opioid use (i.e., administered for acute pain, titrated to effect, and properly monitored by prescribing clinician) in children and adolescents results in an increased risk of opioid addiction.

Of course, there is a real, albeit very small, risk of chemical dependence following opioid prescription—but this cannot result in withholding administration of opioids to children in severe acute pain. This very rare side effect should be addressed using an approach similar to that used to address other opioid-induced adverse effects.

Pseudo-Addiction is a term that describes the clinical scenario caused by under-dosing. If a child in severe pain receives too little opioid, his or her pain will be insufficiently managed and the child will likely ask for more opioids. As
a result, this might be incorrectly interpreted by parents or medical staff as “I think (s)he has become addicted—all (s)he asks for is his/her morphine.” In fact, this child is simply under-treated.

H.2 Myth #2: Opioids Lead to Over-Sedation

When a child in severe acute pain receives a starting dose of an opioid (titrated to effect), he or she will be unlikely to experience respiratory depression. Obviously, if the same child were to receive the same amount of an opioid without underlying acute pain (or significant dyspnea), the risk of over sedation or respiratory depression would be fairly significant.

While a starting dose of an opioid is rather unlikely to induce severe apnea (in contrast to the possible occurrence of somnolence and drowsiness), all children started on opioids or after dose increases need to be carefully observed. Regardless of which opioid is administered to children in severe acute pain, none is without adverse effects to a minority of the population. In our experience, more than 10% of children receiving a particular opioid may display opioid-induced side effects such as somnolence, drowsiness, pruritus, nausea, etc., due to this particular opioid and will require either a dose reduction (if good analgesia) or opioid rotation (if poor analgesia or medium-severe distressing side effects) to another opioid at equianalgesic doses.

Not infrequently, children who had unrelieved pain for more than 12–24 hours have not slept well the preceding nights and tend to "catch up" on their sleep, once their pain is well controlled. Therefore, they may be sound asleep after the administration of morphine or other opioids. As long as vital signs (respiratory rate and oxygenation) remain age-appropriate and the child is able to be aroused and awake and alert in between, over-sedation is less likely.

Coping with pain can be exhausting. This often leads to a period of rest and sleep when pain is finally adequately under control. Once rested and
relieved of pain, many children will become more alert and engaged with others.

**H.3 Myth # 3: Patients and Parents do not Have to Choose Between Poor Pain Control and Over-Sedation**

The goal of opioid administration is to provide excellent symptom control of pain or dyspnea while maintaining function. As mentioned above, true over sedation (versus “picking up sleep”) can be easily managed by opioid rotation (if poor analgesia) or dose reduction (if good analgesia).

Fortunately, in the 21st century, pediatric patients and their parents do not have to choose between poor pain control and sedation. By implementing the above strategies of “broad-spectrum analgesia” (see **H. Figure 1**), we are nearly always able to achieve good analgesia without over sedation.

**H. Figure 1**

Managing Children in Intractable Pain: Broad-Band Analgesia
Blue circles: standard approach; Yellow circles: advanced management in selected cases
H.4 Myth #4: To Avoid Constipation Opioids Should not be Administered

Constipation is the most common adverse opioid-induced side effect and is the only side effect patients do not develop tolerance for. It is imperative therefore that any patient receiving scheduled opioids must have a bowel regimen in place to avoid constipation:

- **Mush & Push:** This includes a scheduled stool softener (“mush”) such as lactulose or Polyethylene Glycol (PEG) 3350 and scheduled or as-needed stimulant laxatives (“push”), such as senna. It may also require prn suppository or enema (“unplugging”). If children experience abdominal pain because of constipation, clearly opioids would not be advantageous but will worsen the underlying problem.
• **Low-dose naloxone:** When opioids bind to a mu-receptor, G-proteins are uncoupled as a result. More specifically, inhibitory Gi/0-Proteins initiate the analgesic effect, and stimulatory Gs-Proteins induce many of the opioid-induced side effects. However, Gs-Proteins are by factor 10–100 times more sensitive to naloxone than Gi/0-Proteins. Therefore, at very low-doses (0.5–2 mcg/kg/h i.v. infusion) opioid-induced side effects such as pruritus, nausea, constipation, etc., can be managed in a large (but not all) number of children without inducing an anti-analgesic effect (expected at normal-dose naloxone).

• **Hypomotility of the gut:** Hypomotility or development of a (sub-) ileus may in fact be an occasional side effect of opioid administration. However, that should not translate into denying opioids to children in severe acute pain who experience abdominal disease. As with the risk of respiratory depression outlined above, careful titration is required and when gut hypomobility as a result of opioid administration might cause clinical problems, the administration of low-dose naloxone, non-opioid analgesics, and/or opioid rotation should be considered.

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**H. References**


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**I. Conclusions**

Nearly all children with cancer will experience severe pain and will usually need strong pain medication, i.e., morphine or other strong opioids. A dose-limiting side effect may require an opioid rotation. Managing intractable pain in
children with advanced cancer will usually require the integration of pharmacology (non-opioids plus opioids—following the WHO-principles) with non-pharmacological, integrative therapies. **(I. Figure 1).** Not uncommonly, children may require the addition of adjuvant analgesia or invasive approaches. Only if all six circles of **I. Figure 1** have been exhausted, and not earlier, would it be necessary to consider sedation to unconsciousness, hence making the latter a very rarely needed intervention (estimated less than once per year in large pediatric cancer care programs).

**I. Figure 1**
Managing Children in Intractable Pain: Broad-Band Analgesia
Blue circles: standard approach, Yellow circles: advanced management in selected cases.

Procedural pain management in children must include the following four “non-negotiable” essential components:

- Positioning
- Distraction
• Topical Anesthesia
• Sucrose (for 0–12 months of age)

If excellent analgesia cannot be achieved by the above means (or cannot be integrated in the currently existing clinical setting yet), consider the addition of analgesia (e.g., intranasal fentanyl) and/or an appropriate level of sedation: Depending on the procedure ranging from minimal sedation (e.g., nitrous gas) to moderate or even deep sedation (ketamine, propofol). In analgesic dosing, we would not expect over sedation. Patients and their parents do not have to choose between an awake and responsive child in pain and an over-sedated child. Nearly always, it is possible to provide good to excellent analgesia without over sedation.

I. Additional Resources

I. Table 1
Equianalgesic methadone chart.

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Estimated Daily Oral Methadone Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gazelle G (2002)</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.epers.msw.edu">www.epers.msw.edu</a></td>
</tr>
<tr>
<td></td>
<td>ROXANE LABORATORIES, INC.</td>
</tr>
<tr>
<td></td>
<td>Columbus, OH 43216</td>
</tr>
<tr>
<td></td>
<td>Toomey JD (2004)</td>
</tr>
<tr>
<td></td>
<td>American Family Physician 71(7):1353-8</td>
</tr>
<tr>
<td>&lt; 100 mg</td>
<td>3:1</td>
</tr>
<tr>
<td></td>
<td>20% - 30%</td>
</tr>
<tr>
<td></td>
<td>33 %</td>
</tr>
<tr>
<td>101mg - 300mg</td>
<td>5:1</td>
</tr>
<tr>
<td></td>
<td>10% - 20%</td>
</tr>
<tr>
<td></td>
<td>20 %</td>
</tr>
<tr>
<td>301mg - 600mg</td>
<td>10:1</td>
</tr>
<tr>
<td></td>
<td>8% - 12%</td>
</tr>
<tr>
<td></td>
<td>10 %</td>
</tr>
<tr>
<td>601mg - 800mg</td>
<td>12:1</td>
</tr>
<tr>
<td></td>
<td>5% - 10%</td>
</tr>
<tr>
<td></td>
<td>8 %</td>
</tr>
<tr>
<td>801mg - 1000mg</td>
<td>15:1</td>
</tr>
<tr>
<td></td>
<td>5% - 10%</td>
</tr>
<tr>
<td></td>
<td>7 %</td>
</tr>
<tr>
<td>&gt; 1000mg</td>
<td>20:1</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td></td>
<td>5 %</td>
</tr>
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</table>
## I. Table 2
Adjuvant analgesia in neuropathic pediatric pain management (Pain Medicine & Palliative Care, Children’s Hospitals and Clinics of Minnesota).

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Comments/side effects (see text for further details)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic Antidepressants (TCA)</td>
<td>Amitriptyline</td>
<td>Starting dose 0.1 mg/kg QHS, usually slowly titrated up to 0.5 mg/kg (max 1-2mg/kg)</td>
<td>PO</td>
<td>Tertiary amine TCA; stronger anticholinergic side effects (incl. sedation) than nortriptyline</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>Starting dose 0.1 mg/kg QHS, usually titrated up to 0.5 mg/kg (max 1 mg/kg)</td>
<td>PO</td>
<td>Secondary amine TCA; anticholinergic side effects</td>
</tr>
<tr>
<td>Gabapenoids</td>
<td>Gabapentin</td>
<td>Starting dose 2 mg/kg QHS, usually slowly titrated up to initial target dose of 6 mg/kg/dose TID (max 300 mg/dose TID). Max. dose escalation to 24 mg/kg/dose TID (max. 1200 mg/dose TID)</td>
<td>PO</td>
<td>Slow dose increase required; side effects: ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td>Starting dose 0.3 mg/kg QHS, usually slowly titrated up to initial target dose of 1.5 mg/kg/dose BID (max 75 mg/dose BID). Max. dose escalation to 6 mg/kg/dose BID (max. 300 mg/dose BID)</td>
<td>PO</td>
<td>Switch from gabapentin, if distressing side-effects or inadequate analgesia. Side effects: ataxia, nystagmus, myalgia, hallucination,</td>
</tr>
<tr>
<td>Condition</td>
<td>Medication</td>
<td>Dosage/Details</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, peripheral edema; Associated with weight gain</td>
<td>Sodium Channel Blocker / Local anesthetic</td>
<td>Lidocaine 5% Max. of 4 patches (in patients &gt; 50kg) 12 hours on/12 hours off Transdermal patch</td>
<td>Not for severe hepatic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>Glucocorticoid</td>
<td>Dexamethasone 0.1 - 1.5 mg/kg (max. 10mg) starting dose, then 0.1 - 0.25 mg/kg x2/day (for &lt; 14 days). [Malignant spinal cord compression (adult dose): Dexamethasone 16-96 mg/day or equivalent]</td>
<td>PO, IV Add gastro-protective agent</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>NMDA-Receptor Anatagonist Ketamine (racemic mixture of S(+)/R(−) enantiomers)</td>
<td>IV: 0.06-0.3 mg/kg/hr PO: 0.2-0.5 mg/kg TID-QID and PRN</td>
<td>IV, PO, (sc, sl, intranasal, pr, spinally) Typical side effects rare at low-dose, but would require benzodiazepine administration</td>
<td></td>
</tr>
</tbody>
</table>

I. Figure 1

Faces Pain Scale Revised (FPS-R) ¹

Please check the web site: [www.painsourcebook.ca](http://www.painsourcebook.ca) for correct administration and translations into many languages of these instructions.
I. References