The Management of Pain in Children with Life-limiting Illnesses

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Despite increasing awareness about causes and treatment of pain in children, at the beginning of the 21st century most children with advanced illness still experience pain. Multiple studies have shown that children have suboptimal pain control in the last days of life [1–6]. Although there are discrepancies in the percentage of time and the degree to which it occurs, there is clear room for improvement in the management of pain in children with life-limiting illnesses. The treatment of pain not only affects the child, but can also have a significant impact on the family [2,7,8].

Pain can be somatic, visceral, or neuropathic in nature and can be disease-related, treatment-related, or caused by spiritual or psychologic distress. The key to effective pain control is obtaining a detailed assessment, developing a child-specific treatment plan, and frequently re-evaluating to determine efficacy.

This article focuses on topics common to practitioners caring for children with life-limiting illnesses. These topics include a review of myths and obstacles to achieving adequate pain control, a review of the pathophysiology of pain, an overview of the use of opioids in children, an approach to the management of neuropathic pain, and a brief discussion of nonpharmacologic pain management strategies. As pediatric palliative medicine providers, the authors have found these topics to encompass the most common situations encountered. Clearly, there are many other aspects important to the
management of pain in this patient population, including assessment and management of emotion and spiritual pain, and the use of more advanced pain regimens, including regional anesthesia techniques.

**Myths and obstacles to good pain control**

No parent or health care provider wishes a child to suffer pain unnecessarily. The pain suffered by children during their illness, regardless of the cause, is a significant source of distress for parents. Why then does there seem to be reluctance to manage pain aggressively? The barriers that health care professionals encounter from both family members and colleagues in aggressively managing pain needs to be highlighted.

For many parents, the words “morphine” or “methadone” conjure up societal, cultural, and familial beliefs that they may or may not discuss with their child’s health care team. In qualitative surveys, concerns parents have voiced regarding their reluctance to use opioids for pain control have included [1,3,9,10]:

- Fear of giving up
- Misconceptions of opioids as “too strong for children”
- Fear of side effects
- Worry their child will become “addicted” to pain medications
- Cultural or religious beliefs

In addition to parental hesitation, health care providers have also expressed reluctance to manage pain with opioids. Reasons cited have included [11,12]:

- Lack of sufficient education regarding managing pain
- Misconceptions about frequency and severity of side effects, such as respiratory depression
- Worries that opioids will shorten life expectancy
- Concerns that escalating opioid doses will increase the likelihood of tolerance, and thus make pain control more difficult as the disease progresses

**Pathophysiology in brief**

To better understand pediatric pain management strategies, it is important to have a basic understanding of the pathophysiology of pain. In general, pain can be broadly divided into categories based on likely pathophysiology. The main categories managed in pediatric palliative care include noxious pain, visceral, and neuropathic pain.

Nociceptive pain is used to describe pain that is related to the degree of receptor stimulation by processes causing tissue injury. Peripheral nociceptors are activated by noxious stimuli, which causes impulses to be transmitted to the spinal cord and higher centers within the central nervous system.
Peripheral nociceptors have various response characteristics and can be found in skin, muscle, joints, and some visceral tissues. Nociception consists of four processes: transduction, transmission, perception, and modulation.

**Transduction**

The nociceptive process begins with transduction (depolarization) at the peripheral nociceptors in response to noxious stimuli.

**Transmission**

Transmission is the process by which these stimuli proceed along primary afferent axons via myelinated A-D fibers and nonmyelinated C fibers to the spinal cord, and then on to higher centers in the brain.

**Perception**

Perception refers to the process when impulses reach higher centers and the individual recognizes pain.

**Modulation**

A very complex system exists to modulate and inhibit pain perception. This involves mediation by the binding of endogenous opioid compounds to subsets of receptors: mu, delta, and kappa. These endorphins are widely distributed and tied to systems regulating pain and stress. In addition, other neurotransmitters, such as serotonin and norepinephrine, also play a role in the endogenous pain modulating system through structures such as descending inhibiting pathways.

Nociceptive pain can be further classified as somatic or visceral. Somatic pain is characterized by being well localized and described as aching, squeezing, stabbing, or throbbing. Bone pain caused by cancer metastasis is an example of somatic pain. Pain arising from stimulation of afferent receptors in the viscera is referred to as “visceral” pain. Visceral pain is not evoked from all organs and is not always associated with direct visceral injury. It is characterized as diffuse and poorly localized, and described by patients as dull, crampy, or achy.

**Management strategies**

The cornerstone to effective pain management in palliative care patients is a repetitive approach involving a detailed assessment of the pain, a patient-specific multimodal treatment plan, and regular, frequent re-evaluation. Clinicians managing pain in children benefit from a consistent approach and a set of tools that they use often and can modify based on
individual clinical situations. One commonly used approach comes from the World Health Organization (WHO). To address some of the confusion surrounding pain treatment for children, and encourage the use of opioids when necessary, the WHO developed a simple stepwise approach to the management of pain in children with cancer, called the “WHO three-step analgesic ladder” [14–16]. Under the assumption that pain would increase as the child’s disease progresses, the goal was to give providers steps to follow to escalate treatment, using progressively stronger analgesics. The first step for the treatment of mild pain uses nonopioid analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), with or without adjuvant pain medications. For more moderate pain, or pain not relieved with the previous medications, weak opioids, such as codeine or tramadol, are added. For severe pain, strong opioids, such as morphine, oxycodone, hydromorphone, or fentanyl are used. Limitations to the initial WHO approach include its lack of utility in neuropathic pain syndromes, its emphasis on the use of opioids to control pain, and the absence of supportive, behavioral, and cognitive methods for alleviating pain. For this reason, the authors use a slightly modified form of the ladder to eliminate this confusion, as shown in Fig. 1.

In addition to the stepwise approach to medications, the WHO pain management guidelines for children with cancer and children receiving palliative care consists of four concepts: “by the ladder,” “by the clock,” “by the mouth,” and “by the child.” The basic premise is that treatment should be escalated according to the WHO three-step analgesic ladder approach outlined above, be administered on a scheduled basis to provide stable blood concentrations with rescue doses as needed, be given by the most appropriate route (which is usually the least invasive most convenient route, such as oral, sublingual, transmucosal, transdermal, or rectal), and be tailored to the individual child’s circumstance, needs, and response to treatment.

Fig. 1. Three-step analgesic ladder. Based on the World Health Organization “three step ladder” approach to cancer pain management. PCA, patient-controlled analgesia.
Pain assessment in children

The first step in aggressive pain management, regardless of whether the practitioner chooses to use the guidelines above, is an accurate age appropriate assessment of the child’s pain. This involves obtaining a thorough evaluation, including a detailed assessment and physical exam. Components in a detailed pain assessment are listed in Table 1.

Most hospitals have standard pain assessment tools that are incorporated into daily practice. Behavioral scores for infants, young children, and children who are cognitively impaired are available [17–22]. Examples are listed in Tables 2–4. For older children, self-report scores, such as faces, numerical rating, or visual analog scales are widely used (Fig. 2). When using these scales, it is important to recognize their limitations to interpret their results. Behavioral scales can often incorporate fear or anxiety and make the result difficult to interpret. Self-report scores can be used too literally, where a child’s pain is considered severe only if the number reported is greater than a four or five. For some patients, lower numbers may signify severe pain. The authors have found the use of standardized pain assessments extremely valuable in assessing the efficacy of a pain intervention and in heightening the awareness of the health care team in the importance of measuring pain. Lastly, for most children, especially those with life-limiting illnesses, pain is multidimensional. The assessment of emotional,

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of primary illness</td>
<td>Primary disease</td>
</tr>
<tr>
<td></td>
<td>Other potential causes of pain (ie, treatment related, procedures)</td>
</tr>
<tr>
<td>Detailed description of pain</td>
<td>Location</td>
</tr>
<tr>
<td></td>
<td>Intensity</td>
</tr>
<tr>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td></td>
<td>Exacerbating factors</td>
</tr>
<tr>
<td></td>
<td>Relieving factors</td>
</tr>
<tr>
<td></td>
<td>Associated symptoms</td>
</tr>
<tr>
<td>Experience with pain medications</td>
<td>Current pain medication regimen, including adjuvant medications, doses, interval</td>
</tr>
<tr>
<td></td>
<td>Side effects experiences, currently and in the past, from pain medications</td>
</tr>
<tr>
<td>Integrative (nonpharmacologic) strategies</td>
<td>Patient’s perception of efficacy of medication</td>
</tr>
<tr>
<td>Parent personal experience with pain medications</td>
<td>Relaxation, acupuncture, hypnosis, distraction, parent’s touch, etc.</td>
</tr>
<tr>
<td>Social factors</td>
<td>Discuss parental bias toward certain medications</td>
</tr>
<tr>
<td>Spiritual factors</td>
<td>Which route would be most convenient and culturally appropriate for child and family</td>
</tr>
<tr>
<td>Influence on medication choice or treatment plan</td>
<td></td>
</tr>
</tbody>
</table>

Table 1
Components of pain assessment in children
psychologic, or spiritual pain is rarely incorporated into standardized pain
assessment tools. Practitioners caring for these children must be aware of
these dimensions of pain and their relationship to the child’s physical pain.

The use of opioids

Opioids are the mainstay for pain management in children at the end of
life. As discussed above, obstacles from the patient, child, and provider can
cause inadequate doses to be used in children [3,11].

Opioids work at many different receptors, including the five opioid recep-
tors: mu, kappa, sigma, delta, and epsilon. Opioids work at the supraspinal
and spinal levels and outside the central nervous system. When opioids
attach to receptors at the spinal level or in the peripheral nervous system,
they modify the transmission of painful signals, diminishing pain perception
[23–25]. Each opioid may act at several receptors. At the supraspinal level,
ioopioid receptors send descending inhibitory signals that modify incoming
pain signals at the synaptic spinal level. In addition to inhibiting painful
signal transmission, opioids work in the limbic system, which alters
emotional response to pain. Each opioid has different affinities for different
receptors, so patients may have different responses to different opioids with
great intraindividual variability (Tables 5–7) [26,27].

Commonly used opioids in palliative care patients

Morphine

Morphine is the most commonly used and well-studied opioid used to
treat moderate and severe pain in pediatric palliative care patients. As the
most well studied of the opioids, much is known about its pharmacokinetics
and side effects. Studies in pediatric patients have demonstrated both its
safety and efficacy [17,28,29]. Morphine is an opioid receptor agonist that
binds and activates the $\mu$-opioid receptors in the central nervous system.

Table 3
Pediatric pain assessment scale for children who have difficulty verbalizing pain

<table>
<thead>
<tr>
<th>FLACC SCALE</th>
<th>Categories</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 = $</td>
<td>Relaxed/comfortable</td>
<td>Occasional grimace or frown, withdrawn, disinterested</td>
</tr>
<tr>
<td>$1–3 =$</td>
<td>Mild discomfort</td>
<td>Uneasy, restless, tense</td>
</tr>
<tr>
<td>$4–6 =$</td>
<td>Moderate pain</td>
<td>Kicking, or legs drawn up</td>
</tr>
<tr>
<td>$7–10 =$</td>
<td>Severe pain</td>
<td>Arched, rigid or jerking</td>
</tr>
</tbody>
</table>


most well studied of the opioids, much is known about its pharmacokinetics
and side effects. Studies in pediatric patients have demonstrated both its
safety and efficacy [17,28,29]. Morphine is an opioid receptor agonist that
binds and activates the $\mu$-opioid receptors in the central nervous system.
The activation of these receptors leads to euphoria, sedation, analgesia,

Table 4
Additional pediatric pain assessment scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Age</th>
<th>Indicators</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEOPS (Children’s Hospital of Eastern Ontario Pain Scale)</td>
<td>1–7 years</td>
<td>Cry, facial expression, verbalization, torso movement, if child touches affected site, position of legs</td>
<td>$\geq 4$ signifies pain</td>
</tr>
<tr>
<td>NIPS (Neonatal/Infants Pain Scale)</td>
<td>Infants $&lt; 1$ year</td>
<td>Facial expression, cry, breathing pattern, arms, legs, and state of arousal are observed for 1-min intervals before, during, and after a procedure</td>
<td>$&gt; 3$ indicates pain</td>
</tr>
</tbody>
</table>
physical dependence, and respiratory depression. Almost all morphine is converted by hepatic metabolism to the 3- and 6-glucuronide metabolites (M3G and M6G). M6G has been shown to have a much stronger analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity [30,31]. Elevated concentrations of M3G as well as M3G/M6G ratios may play a role in hyperalgesia, allodynia, and myoclonus [32,33]. In patients who develop these side effects, it may be beneficial to switch to a structurally dissimilar opioid, such as methadone or fentanyl, to allow M3G to clear from the cerebral spinal fluid. Morphine can be given orally, sublingually, subcutaneously, intravenously, rectally, intrathecally, or via an epidural. The oral form comes in both an immediate release and sustained release preparation. It is important to remember that there is an increased half-life and diminished clearance in neonates that can produce a higher risk of respiratory depression. Thus the dose and dose intervals should be modified and titrated appropriately.

**Hydromorphone**

Hydromorphone has very similar properties to morphine. It is given in the same routes, although a long acting form is currently not available in the United States. Hydromorphone is more lipid soluble and more potent than morphine, but it is unclear what practical advantages exist. Adult
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Metabolism</th>
<th>Metabolites</th>
<th>Elimination route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Cytochrome P-450 2D6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Codeine-6-glucuronide</td>
<td>Renal</td>
<td>Oral bioavailability 15%–80%; slow-metabolizers don’t produce the active metabolite morphine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norcodeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine (&lt;10% -may account for analgesic properties of codeine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Morphine-3-glucuronide (55%–75%); acts as a neuroexcitatory agent; contributes to adverse morphine effects such as myoclonus and confusion</td>
<td>Renal</td>
<td>Metabolites have a very extended half life in patients with renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine-6-glucuronide (5%–15%); exhibits opioid activity; up to 40 times more potent than morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Cytochrome P-450 2D6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hydromorphone-3-glucuronide</td>
<td>Renal</td>
<td>Literature states no opioid active metabolite; however anecdotal evidence of increased neurotoxicity or renal failure with very high doses</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Cytochrome P-450 3A4</td>
<td>Noroxycodone—major metabolite; weak mu agonist</td>
<td>Renal, hepatic</td>
<td>Unlike codeine oxycodone is a potent analgesic itself</td>
</tr>
<tr>
<td></td>
<td>Cytochrome P-450 2D6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oxymorphone (minor metabolite with marked opioid activity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noroxymorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Cytochrome P-450 3A4</td>
<td>Norfentanyl—inactive</td>
<td>Renal, hepatic</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>

<sup>a</sup> Metabolism affected by genetic polymorphisms in CYP 2D6 and drug interactions. It is estimated that 5% to 10% of Caucasians are CYP2D6 poor metabolizers.

*Data from* Refs. [26,27,24].
studies have not shown clear benefit over the use of morphine. It is metab-
olized in the liver by cytochrome P450 2D6 [34]. There have been some stud-
ies describing the drug’s pharmacokinetics and metabolism in children
[35,36]. It is advertised not to have any active opioid metabolites, which
would improve its safety in patients with renal failure [37]. However, hydro-
morphone-3-glucoronide is a detectable metabolite and there is anecdotal
evidence, including the authors’ experience, that there is an increased neuro-
toxicity and incidence of jerking on high doses, especially in children with
compromised renal function. Fentanyl or methadone are likely to be better
choices in children with renal failure.

**Fentanyl**

Fentanyl is highly lipophilic and 80 to 100 times more potent than
morphine in adults, less so in younger children (in neonates 13–20 times
as potent). It is the only opioid available in a transdermal preparation in
the United States, which makes it very useful in the palliative care patients
who cannot take oral medications. Fentanyl has a shorter onset of action
and shorter duration of action than morphine [38]. This has made the
drug useful in conscious sedation for procedures in pediatric patients [39].
According to small studies, the pharmacokinetic parameters are similar in
children as for adults [40,41]. The isoenzyme cytochrome P<sub>450</sub> 3A4 (CYP
3A4) metabolises fentanyl in the liver and intestinal mucosa into the phar-
macologic inactive metabolite norfentanyl, which is then eliminated by the
kidney. Potent inhibitors of CYP 3A4, such as macrolide antibiotics (eg,
erythromycin), certain protease inhibitors (eg, ritonavir), antimycotics (eg,
ketoconazole), and grapefruit juice may decrease the systemic clearance of
fentanyl, which may result in increased or prolonged opioid effects. When
compared with other opioids, fentanyl is a relatively safe drug and adverse

<table>
<thead>
<tr>
<th>Medication</th>
<th>Parenteral dose (mg)</th>
<th>Oral or rectal dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td>Fentanyl (*)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5–2</td>
<td>6–8</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>15–20</td>
</tr>
<tr>
<td>Methadone</td>
<td>10 mg</td>
<td>10 mg–20 mg</td>
</tr>
</tbody>
</table>

Converting patients from one opioid to methadone requires close observation for delayed
sedation, which may occur 3 to 5 days following the initiation of the drug. Dose intervals
need to be decreased after the initial 1 to 2 days of treatment to avoid late sedation.

* A child must be tolerant to 30 mg–60 mg per 24 hours oral morphine equivalent to be
rotated to the smallest Fentanyl patch (12.5 mcg/hr). Conversion from oral morphine per
drug supplier: 25 μg/h (oral morphine 30 mg/day–135 mg/day) 50 μg/h (135 mg/day–224 mg/
day) 75 μg/h (225 mg/day–314 mg/day) 100 μg/h (315 mg/day–404 mg/day).
reactions are typical of the opioid group of drugs [42]. All patients receiving fentanyl must be monitored for respiratory depression, which may initially manifest as somnolence. Clinically significant respiratory depression can be antagonised with naloxone. Circulatory depression, hypotension, and shock seem to be caused less often by intravenous fentanyl than by other opioids. Thoracic rigidity may follow a rapid bolus of high dose intravenous fentanyl (greater than 5 mg/kg–15 mg/kg). This can be treated with naloxone, but may require a muscle relaxant.

It is also important to note that when using fentanyl as an infusion, tolerance may develop more quickly than with other opioids. Limitations of this medication include that the transdermal patch comes in set increments, which makes titration difficult. Routes of application include intranasal, intravenous, subcutaneous, sublingual, oral transmucosal, and transdermal.

Fentanyl patches must not be introduced as the first opioid in the treatment of pain and it cannot be used to manage the pain of opioid-naïve children. Because of a long onset time, inability to rapidly titrate drug delivery and long elimination half-life, transdermal fentanyl is contraindicated for acute pain management. It is better used for chronic, stable pain in the setting of an opioid rotation or finding an alternative route of administration.

Oxycodone

Oxycodone has similar properties to morphine. The pharmacokinetics of oral oxycodone differs from oral morphine in that it has a higher bioavailability, a slightly longer half-life, and is hepatically metabolized by cytochrome P450 to both active and inactive metabolites [25, 43–45]. Noroxycodone is the major metabolite but has much weaker activity than oxycodone. The other significant metabolite, oxymorphone, is present in much smaller amounts but has potent opioid properties. Oxycodone is a mu and kappa opioid receptor agonist and its analgesia is characterized by a rapid onset of action without an analgesic ceiling. The relative potency of oral oxycodone is between 1.5 and two times that of oral morphine. Its doses can be escalated to effect even to very high doses. It has been shown that in children, clearance of the drug is up to 50% higher with a lower volume of distribution [46]. It comes in both an immediate release and sustained release formulation. There have been no significant safety studies in pediatrics using the extended release formulation. In addition, it is available both with and without acetaminophen.

Codeine

Codeine is often listed as a weak opioid. It is metabolized in the liver to morphine. However, it has been shown in recent literature that conversion
<table>
<thead>
<tr>
<th>Drug</th>
<th>Routes</th>
<th>Oral dose</th>
<th>Parenteral dose</th>
<th>Infusion starting doses</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>PO</td>
<td>0.5 mg/kg–1 mg/kg codeine q 4–6 h (watch for acetaminophen doses to avoid toxicity)</td>
<td>N/A</td>
<td>N/A</td>
<td>Soln: 3 mg/mL Tabs: 15 mg, 30 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV, Transdermal</td>
<td>N/A</td>
<td>0.5 mcg/kg–1 mcg/kg q 15–30 minutes</td>
<td>Init: 1 mcg/kg Basal: 0.5 mcg/kg/hour–1.5 mcg/kg/hr</td>
<td>Patches: 12.5 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h</td>
</tr>
<tr>
<td></td>
<td>SQ, Buccal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intranasal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO</td>
<td>0.03 mg/kg/dose–0.06 mg/kg/dose q 3–4 hr (&gt;50 kg: 1 mg–2 mg q 3–4 hr)</td>
<td>0.015 mg/kg/dose q 3–4 hr</td>
<td>Init: 0.003 mg/kg/dose Basal: 0.003 mg/kg/h–0.005 mg/kg/hr</td>
<td>Inj: 2 mg/mL Tab: 2 mg, 4 mg, 8 mg</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SQ, SL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>PO</td>
<td>Oral (Immediate release) &gt;6mos: 0.15 mg/kg/dose–0.3 mg/kg/dose q 3–4 hr</td>
<td>0.05 mg/kg/dose–0.1 mg/kg/dose q 3–4 hr</td>
<td>Init: 0.01 mg/kg/dose–0.02 mg/kg/dose</td>
<td>IV: 2 mg/mL, 15 mg/mL</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PR, SQ, IV</td>
<td></td>
<td></td>
<td></td>
<td>Tabs (IR): 15 mg Tabs (SR): 15 mg, 30 mg, 60 mg, 100 mg Soln: 10 mg/5 mL, 20 mg/mL</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Dose/Range</td>
<td>Additional Notes</td>
<td>Solna</td>
<td>Tablets</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>0.1 mg/kg - 0.2 mg/kg q 4 h</td>
<td>Adults: 5 mg – 10 mg q 4 h</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>PO</td>
<td>1–2 mg/dose q 4 h; max. of 8 mg/kg/day (&gt; 50 kg max 400 mg/day)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note that these merely represent starting doses, which need to be titrated to effect. Some children will require significantly larger doses to experience good pain control.
from codeine to the active analgesic form of morphine is suboptimal in the pediatric population and more than 10% of the white Caucasian population are slow metabolizers for the cytochrome P450 2D6, hence are unable to metabolize the prodrug codeine to morphine. This makes its use in the palliative care population, who often have moderate to severe pain, problematic [25,47]. Codein comes only with acetaminophen in the United States and is available in both liquid and pill forms. Its benefit is that it is widely available and most practitioners and parents are familiar with the medication.

Methadone

Methadone is a unique long acting opioid that is a racemic mixture of two isomers. One acts primarily as a mu opioid and the other as an antagonist at the N-methyl-aspartate receptor in the brain, spinal cord, and peripheral nerves. It has a high oral bioavailability with slow metabolism in the liver [25,47–51]. Metabolites are inactive. It has a long and sometimes unpredictable half life ranging from 12 hours to almost 200 hours. To complicate things further, the duration of analgesia is much shorter than the half life, which requires dosing to be more frequent initially. This can cause delayed sedation and potentially life threatening respiratory depression. Because it comes in a liquid formulation, methadone can be used as an extended pain medication for children unable to swallow pills. However, it should be noted that little data is available regarding the pharmacokinetics in young children and infants [52,53]. In addition, conversion from standard opioids is highly dependent on the individual patient’s metabolism and tolerance. The authors have found this medication extremely useful in the pediatric palliative care population when used cautiously. As mentioned below, it can be used in the management of neuropathic pain.

Managing opioid side effects

Opioids generally have a similar side effect profile. Side effects are common and, if left untreated, can greatly impact on the patient’s quality of life [54–56]. It is important to be aware of the common opioid side effects and treat them aggressively [23,33,55,57]. Table 8 lists common side effects as well as management suggestions.

Adjuvant medications

Adjuvant pain medications are medications whose primary indication is not to treat pain, but that may have analgesic properties in specific circumstances. In the pediatric palliative care population, there have been few controlled trials showing significant efficacy. Most practitioners who use adjuvant regimens use anecdotal data or extrapolate from the adult studies. The most commonly used adjuvant medications include those used to treat
<table>
<thead>
<tr>
<th>Side effect</th>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>- Prophylactic stool softener (eg, lactulose)</td>
<td>- Almost universal</td>
</tr>
<tr>
<td></td>
<td>- Stimulant laxative</td>
<td>- Should start prophylactically</td>
</tr>
<tr>
<td></td>
<td>- Low-dose naloxone</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>- Opioid rotation</td>
<td>- Caused by activity at opioid receptors in the chemoreceptor</td>
</tr>
<tr>
<td></td>
<td>- 5-HT3 receptor antagonist</td>
<td>trigger zone. Can decrease after 3–7 days</td>
</tr>
<tr>
<td></td>
<td>- (Phenothiazine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- D2-Receptor Antagonists (eg, Metoclopramide, Haloperidol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Antihistamins (Diphenhydramine, Cyclizine,</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>- Diphenhydramine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Opioid rotation</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>- Opioid rotation; if unsuccessful: psychostimulant trial</td>
<td>- Can decrease after 3–7 days</td>
</tr>
<tr>
<td>Confusion</td>
<td>- Opioid rotation</td>
<td>- Increased with renal or hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>- Or Consider trial of dose reduction</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>- Opioid rotation</td>
<td>- Usually occurs in patients on high dose opioids because of the</td>
</tr>
<tr>
<td></td>
<td>- Benzodiazepine</td>
<td>accumulation of neurotoxic metabolites.</td>
</tr>
<tr>
<td></td>
<td>- Muscle relaxant</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>- Opioid rotation</td>
<td>- Anecdotally less common with fentanyl</td>
</tr>
<tr>
<td></td>
<td>- External bladder pressure</td>
<td>- Use of opioid mixed receptor agonist/antagonist such as</td>
</tr>
<tr>
<td></td>
<td>- Bethanacol</td>
<td>- nalbuphine may cause opioid withdrawal in children</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>- Opioid rotation, if poor pain control</td>
<td>- Much less frequent than commonly thought</td>
</tr>
<tr>
<td></td>
<td>- Decrease dose interval of opioid, if good pain control</td>
<td>- Can be more common in neonates due to longer opioid half</td>
</tr>
<tr>
<td></td>
<td>- Oxygen</td>
<td>- life caused by immature enzyme systems</td>
</tr>
<tr>
<td></td>
<td>- Repositioning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Use opioid receptor antagonents with caution</td>
<td></td>
</tr>
</tbody>
</table>
neuropathic pain and those used for specific disease related pain. Medications specifically for neuropathic pain are described in a later section. Disease related pain includes bone pain secondary to tumor metastasis, fracture, primary bone defects, bowel spasm from obstruction, or muscle pain from neurodegenerative disease, or other chronic diseases, such as cerebral palsy. Tables 9 and 10 [58] show examples of adjuvant pain regimens and dosing strategies for these conditions.

Management of neuropathic pain

The incidence and prevalence of neuropathic pain at the end-of-life of children is unclear, but in the authors’ experience the majority of children or teenagers with cancer or neurodegenerative conditions suffer from this debilitating pain entity. Managing neuropathic pain in pediatric palliative care will likely require an interdisciplinary, holistic approach. This type of pain, not nociceptive in nature, and nonprotective, persists independent of ongoing tissue injury or inflammation. Verbal children may describe the quality of neuropathic pain as burning, shooting, or stabbing, but we are often entranced by the complexity of the child’s own descriptors. It is of utmost importance to differentiate the different pain entities during pain assessment, as nociceptive, neuropathic, visceral, or spiritual pain may be scored by the child quite differently and needs to be treated individually as such. The authors suggest the following approach in managing neuropathic pain in children, which includes evaluation and the treatment of underlying causes through pharmacologic and nonpharmacologic approaches.

Evaluation

After a complete history has been taken, a child needs to be examined thoroughly, which includes a complete neurological examination. Clinical findings may include hyperalgesia, allodynia and cutaneous hyperesthesia, motor dysfunction such as spasms, dystonia and fasciculations, and autonomic changes, such as cyanosis, hyperhidrosis, or swelling [59].

Treatment of underlying causes

Evaluate whether an underlying cause may be treatable in accordance with the treatment goals of the patient and his or her family. Underlying pathologies causing neuropathic pain may include neurodegenerative

Table 9
The use of adjuvant pain medications

<table>
<thead>
<tr>
<th>Disease related pain</th>
<th>Adjuvant pain treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>Bisphosphonate, calcitonin, steroids, radiotherapy</td>
</tr>
<tr>
<td>Bowel spasm</td>
<td>Octreotide, anticholinergic</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>Benzodiazepine, Botulinum toxin A, baclofen</td>
</tr>
</tbody>
</table>
conditions, raised intracranial pressure, postsurgical peripheral neuropathic pain, phantom limb pain, neuroirritability, and metabolic neuropathies. Children with malignancies may experience neuropathic pain caused by all aspects of tumor therapy (such as vinca-alkaloid induced neuropathy) and the tumor itself. Neuropathic pain caused by primary tumor or metastases involvement of the central or peripheral nervous system may respond to radiation, bisphosphonates for bone lesions, corticosteroids, palliative chemotherapy, or surgery. Anxiety, depression, and spiritual pain in the child and his caregivers need to be assessed and addressed.

**Integrative, nonpharmacologic treatment modalities**

State of the art pain management in the 21st century demands that pharmacologic management must be combined with supportive measures and integrative, nonpharmacologic treatment modalities. Physical methods include a cuddle or hug from the family, massage, transcutaneous electrical nerve stimulation, comfort positioning, heat, cold, and especially physical or occupational therapy, as well as rehabilitation. Cognitive behavioral techniques include guided imagery, hypnosis, abdominal breathing, distraction, story telling. Acupressure or acupuncture may be very helpful. An agreed
upon plan of passive, and if possible, active coping skills, needs to be implemented considering the child’s wishes and those of his or her family.

**Pharmacologic approaches**

There are no published randomized controlled trials (RCT) about the management of neuropathic pain in children, let alone in pediatric palliative care. A review of adult RCTs regarding drug approaches to neuropathic pain revealed that with a number-needed to treat (NNT) of 2.5, strong opioids (after carbamazepine – NNT 2.0) have the best evidence of efficacy. The NNT for tricyclic antidepressants was 3.1, lidocaine patch 4.4, gabapentin 4.7, and selective serotonin reuptake inhibitors 6.8 [60]. Traditional teaching that neuropathic pain is unresponsive to opioids cannot be upheld. In the authors’ experience, the majority of children with life-limiting conditions experience a significant improvement of their neuropathic pain following the application of opioids.

**Opioids**

Opioids have become one of the mainstays of therapy in the pediatric management of neuropathic pain at end-of-life care. This is especially true if the pain is caused by tumor invasion of the spine, when doses of more than 1,000-mg intravenous morphine per hour may be required to achieve satisfactory pain control. Reported maximum morphine doses range between 73.9 mg/kg to 518 mg/kg per hour in pediatric palliative care [61–63]. If a dose escalation of morphine does not provide adequate pain control, or causes intolerable adverse effects, one should consider an opioid rotation (eg, to fentanyl, hydromorphone, or oxycodone on equianalgesic doses). Methadone is an opioid particularly useful in the management of neuropathic pain, with its combined activity as mu-receptor agonist and an N-methyl-D-aspartate (NMDA)-receptor antagonist.

**Tramadol**

The authors see a number of children with mitochondrial dysfunction and other degenerative conditions, who seem to experience prolonged episodes of inconsolability, which persist despite a thorough workup and initial management with simple analgesia, benzodiazepines, chloral hydrate, or anticonvulsants. In this subgroup we found the use of tramadol particularly helpful. This weak opioid (a synthetic 4-phenyl-piperidine analog of codeine) has a ceiling effect and a very good safety profile regarding respiratory depression. It is not only a weak mu-receptor antagonist, but also a serotonin and norepinephrine reuptake inhibitor and likely an alpha-2 agonist. This complementary action yields some theoretical benefit in the management of neuropathic and nociceptive pain. However, Finnerup and colleagues [60] rated tramadol in the above cited review merely with a NNT of 3.9.
**N-methyl-D-aspartate-receptor antagonists**

Strong pain stimuli activate NMDA receptors and produce hyper excitability of dorsal root neurons. This induces central sensitization, wind-up phenomenon, and pain memory. NMDA-receptor antagonist may be able to prevent the induction of central sensitizations caused by stimulation of peripheral nociception, as well as block the wind-up phenomenon.

**Ketamine**

Ketamine is an NMDA-receptor antagonist, but has other actions which may also contribute to its analgesic effect, including a mu-, delta-, and kappa-opioid like effect, interactions with calcium and sodium channels, cholinergic transmission, and noradrenergic and serotonergic reuptake inhibition (the latter ensuring intact descending inhibitory pathways necessary for analgesia). Evidence to guide its use at subanesthetic doses is limited and in part contradictory [64]. Pediatric experience has shown that ketamine is effective for the treatment of postoperative and nonsurgical acute nociceptive pain, as well as for neuropathic pain in low, subanesthetic doses, both alone or in combination with opioids [65–70]. Ketamine is unique among anesthetic agents in that it does not depress respiratory and cardiovascular systems. In subanesthetic (analgesic) doses, the typical anesthetic-dose side effects of ketamine, including nystagmus, lacrimation, salivation, tachycardia, and spontaneous movements are usually absent, and the patient can respond and interact coherently. Also, the vivid and oftentimes disturbing dreams and hallucinations are avoided. The clinical spectrum and variability with ketamine is much greater than with most other analgesics. Additionally, while some patients may tolerate enormous doses of the drug with analgesic effect and no systemic side effects, others may have unacceptable side effects at a very low dose before experiencing any analgesic effect.

A large adult meta-analysis of 2,385 patients found that adverse effects were not increased with low-dose ketamine [51]. However, until there is better pediatric data, children should be watched for hypertension, tachycardia, euphoria or dysphoria, and hallucinations. Although one pediatric study could not appreciate an opioid sparing effect of ketamine, there is anecdotal evidence of significant opioid reductions in end-of-life pediatric cancer care with children on high doses of opioids after the initiation of ketamine [71].

The advantage of ketamine in comparison to other frequently used adjuvant analgesia, such as anticonvulsants or antidepressants, is its rather immediate onset of action [72].

**Other N-methyl-D-aspartate-receptor antagonists**

Methadone, as mentioned above, is an example of another NMDA-receptor antagonist (and mu-receptor agonist) frequently used in pediatric palliative care. Methadone’s routes of application include intravenous, oral, subcutaneous, sublingual, and rectal. Other NMDA-receptor
antagonists, such as dextromethorphan, amantadine, and memantine are not commonly used in pediatrics.

*Tricyclic antidepressants*

Tricyclic antidepressants have shown to be effective in the management of neuropathic pain in adults [73]. No pediatric RCTs were published yet. Tricyclic antidepressants exert their analgesic effects by blocking the presynaptic re-uptake of serotonin and norepinephrine, thereby modulating the descending inhibiting pathways. They may also act as NMDA-receptor antagonists.

Common anticholinergic side effects include sedation (hence, to be give once at night), dry mouth, blurry vision, constipation, and urinary retention. Patients should receive an EKG before initiation of therapy to rule out QT-prolonging, Wolfe-Parkinson-White-Syndrome, or other pre-existing rhythm disturbances, as tricyclic antidepressants may bear dysrhythmic qualities. Sudden discontinuation should be avoided.

*Amitriptyline*

Amitriptyline is among the oldest and most commonly used adjuvant analgesic for neuropathic pain in children, although the pediatric evidence is limited [74–77]. The authors use amitriptyline as the first-line tricyclic adjuvant analgesia for neuropathic pain. The sedating effect manifests immediately, which often proves helpful as sleeping through the night is a common problem among this pediatric patient group. The analgesic effect may commence to occur 3 to 7 days after initiation, occasionally even later. If distressing anticholinergic side effects occur, the authors usually reduce the dose by 50% and increase the dose slowly again over several days to weeks.

*Other tricyclic antidepressants*

Several major pediatric centers prefer nortriptyline (alternative: imipramine) with the notion that they may cause fewer anticholinergic side effects than amitriptyline. Desipramine, a secondary amine, may be considered an alternative, if small doses of the tertiary amines amitriptyline, nortriptyline, or imipramine cause over-sedation.

*Anticonvulsants*

*Gabapentin*

Gabapentin is commonly used in pediatric pain management. There are no RCTs and few case reports [78–85]. The exact mechanism of action is unclear, but it acts as a calcium-channel blocker, increases gamma-aminobutyric acid (GABA) synthesis and GABA release. Clinical pediatric experience seems to indicate, that gabapentin and amitriptyline are similar in efficacy. In our center, the authors use it second line to amitriptyline (or in combination). Reasons include its application three times per day, as compared with the tricyclic dose once per night, an (adult) NNT of 4.7, worse than those of
tricyclic antidepressants (NNT of 3.1), and not infrequent incidence of side effects, such as nystagmus, thought disorder, hallucinations, headache, weight gain, and myalgia among the patient population.

To avoid pain or precipitating seizures, this anticonvulsant should be weaned off over one to two weeks.

**Other anticonvulsants**

Data to supporting the efficacy of other anticonvulsants in the management of pediatric neuropathic pain is less robust. Sodium channel modulators, such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, topiramate, lamotrigine, and valproic acid act as modulators of peripheral sensitization. Calcium-channel blockers, apart from gabapentin, include lamotrigine and oxcarbazepine, and inhibit central sensitization. There is no pediatric data on pregabaline.

**Other pharmacological approaches**

**Lidocaine patch**

The lidocaine 5% patch is effective in the management of adult neuropathic pain, including postherpetic neuralgia, painful diabetic neuropathy, painful idiopathic sensory polyneuropathy, and nonpostherpetic peripheral neuropathies (as well as osteoarthritis and lower back pain) [86–93]. There are no pediatric RCTs. The authors found the lidocaine patch useful in selected children.

**Propofol**

The authors have positive experiences in pediatric palliative care using the general anesthetic propofol in subanesthetic doses (starting dose 0.3 mg/kg–1 mg/kg per hour) for managing refractory (neuropathic) cancer pain in children [94].

**Neurourgical interventions and nerve blocks**

A small subgroup of children at the end-of-life may require invasive procedures, such as regional anesthesia (epidural or subarachnoid intrathecal infusions) with opioids, local anesthetics, or the alpha-2-agonist clonidine. Frequently, these agents are administered via an implantable catheter, alleviating the necessity of repeated punctures [95]. Rare interventions, such as implantable drug delivery systems, intraventricular morphine, or percutaneous cervical cordotomy may be considered, if pain is intractable using opioids, adjuvant analgesia, and integrative treatment modalities.

**Nonpharmacologic pain management strategies**

It is clear that pain in children is complex and modified based on the child’s developmental level, temperament, previous experiences with pain,
<table>
<thead>
<tr>
<th>Age</th>
<th>Pain behaviors</th>
<th>Cognitive-behavioral approaches</th>
<th>Complementary therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>• Avoiding eye contact</td>
<td>Use pacifier</td>
<td>Massage</td>
</tr>
<tr>
<td></td>
<td>• Grimacing</td>
<td>Swaddling</td>
<td>Sucrose solution</td>
</tr>
<tr>
<td></td>
<td>• Difficulty sucking</td>
<td>Touch</td>
<td>Aromatherapy</td>
</tr>
<tr>
<td></td>
<td>• High-pitched crying</td>
<td>Distraction</td>
<td></td>
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<tr>
<td></td>
<td>• Quivering chin</td>
<td>Music</td>
<td></td>
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<tr>
<td></td>
<td>• Difficulty calming</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Wanting to be still</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• and ↑ hiccupping</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• and ↑ or ↓ breathing</td>
<td></td>
<td></td>
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<tr>
<td>Toddlers</td>
<td>• Difficulty in sleeping</td>
<td>Story telling</td>
<td>Massage</td>
</tr>
<tr>
<td></td>
<td>• Lose interest in play</td>
<td>Blowing bubbles</td>
<td>Warm/cool compress aromatherapy</td>
</tr>
<tr>
<td></td>
<td>• and ↑ crying</td>
<td>Toys</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• and ↑ irritability</td>
<td>Distraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• and ↑ restlessness</td>
<td>Art &amp; music therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• and ↓ eating or drinking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preschool</td>
<td>• Difficulty sleeping</td>
<td>Distraction (cartoons)</td>
<td>Massage</td>
</tr>
<tr>
<td></td>
<td>• Lose interest in play</td>
<td>Offer favorite toy/object to hold</td>
<td>Reiki</td>
</tr>
<tr>
<td></td>
<td>• Quiet or curled</td>
<td>Art &amp; music therapy</td>
<td>Emotive imagery</td>
</tr>
<tr>
<td></td>
<td>• Need to be held</td>
<td></td>
<td>Warm/cool compress aromatherapy</td>
</tr>
<tr>
<td></td>
<td>• Says something hurts</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ eating or drinking</td>
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</table>
### School-age
- Difficulty sleeping
- Moaning/crying
- Hold or protect area of discomfort
- Lose interest in play
- Decrease activity level
- Complain of pain
- ↓ eating or drinking

Create a safe environment  
Dim lights, decrease noise, approach using a calm manner  
Power of suggestion  
Counting  
Art & music therapy  
Breathing techniques  
Visualization/guided imagery  
Massage  
Reiki  
Progressive muscle relaxation  
Warm/cool compress  
Hypnosis (> 10 y)  
Acupuncture (> 10 y)  
Aromatherapy  
Yoga/meditation/reflexology

### Adolescent
- Increasingly quiet
- Lose interest in friends and family
- Decrease activity level
- ↑ anger or irritability
- Changes in eating habits

Create a safe environment  
Dim lights, decrease noise, approach using a calm manner  
Distraction  
TV, video game, read a book, music  
Art & music therapy  
Breathing techniques  
Visualization/guided imagery  
Massage  
Reiki  
Warm/cool compress  
Hypnosis  
Acupuncture  
Aromatherapy  
Yoga/meditation/reflexology
anxiety, and other sources of distress, both physical, emotional, and spiritual. The use of nonpharmacologic interventions in pain management strategies is crucial. Simple techniques, such as distraction and environmental changes, along with more complex cognitive behavioral therapies can be invaluable [96–99]. Table 11 lists examples of nonpharmacologic pain management strategies based on a child’s age [98,100,101].

Summary

The management of pain in children with life-limiting illnesses is complex and, unfortunately, often not done effectively yet. Pain is a multidimensional symptom that can overshadow all other experiences of both the child and family. Frequent pain assessments and flexible treatment plans are essential. Further studies to better understand the safety, pharmacology, and effectiveness of medications used to treat pain in children is necessary. In addition, further exploration into the assessment and management of the emotional and spiritual components of pain needs to be done in this population. The authors believe that with an aggressive, consistent, and knowledgeable approach, pain suffered by children with life-limiting illnesses, regardless of etiology, can be treated effectively.

Acknowledgments

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References


PAIN IN CHILDREN WITH LIFE LIMITING ILLNESSES