Ensuring pain relief for children at the end of life

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M-C Grégoire, G Frager. Ensuring pain relief for children at the end of life. Pain Res Manage 2006;11(3):163-171.

Pain management in the context of pediatric palliative care can be challenging. The present article reviews, through a case-based presentation, the nonpharmacological and pharmacological methods used to ensure adequate pain control in children facing end of life. Details on the impressive range of opioid dosages required and routes of administration are highlighted from published literature and clinical experience. Where available, evidence-based recommendations are provided. Potential side effects of pain medication and barriers to good pain control are discussed. Novel analgesics and innovative delivery methods are presented as future tools enhancing pain relief at the end of life. Some challenges to ethically grounded research in this important context of care are reviewed.

Key Words: *Children; End of life; Opioids; Pain, Palliative care; Pediatric*

Le soulagement de la douleur pour les enfants en fin de vie

La prise en charge de la douleur peut être complexe en soins palliatifs pédiatriques. Le présent article analyse, par une présentation de cas, les méthodes non pharmacologiques et pharmacologiques utilisées pour assurer un contrôle adéquat de la douleur chez les enfants en fin de vie. Les détails de la gamme impressionnante de doses d'opiacés nécessaires et des voies d'administration proviennent de publications et de l'expérience clinique. Lorsqu'elles sont disponibles, des recommandations probantes sont fournies. Les réactions indésirables potentielles des analgésiques et les obstacles à un bon contrôle de la douleur sont abordés. De nouveaux analgésiques et de nouveaux modes d'administration sont présentés comme de futurs outils pour mieux soulager le contrôle de la douleur en fin de vie. Certains défis à des recherches éthiques dans ce contexte d'importance sont également passés en revue.

Although applicable to pain management and palliative care broader than that faced at the end of life, the present article is largely focused on this narrower context of care. Pediatric palliative care is defined as the active and total approach to care, embracing physical, psychological and spiritual elements, focusing on enhancement of quality of life for the child and support for the family (1). It is not limited to end-of-life or terminal care but rather has a broader, more inclusive approach and integrates palliative care concurrently with curative-oriented goals. There is a wide range of life-threatening diseases affecting children, and the palliative care team may be involved for years. The present article focuses on the management of pain at the end of life, which may extend from days to months. The understanding necessary within the team to ensure excellence when caring for infants, children and adolescents at the end of life is highlighted. Aspects of pain assessment are largely addressed by other authors within this special section of *Pain Research & Management*.

Children of all countries are faced with life-threatening conditions. In North America, more than one-half of pediatric deaths occur in children younger than one year of age, with congenital malformations, chromosomal abnormalities, and disorders related to prematurity or low birth weight constituting the main causes (2). For the older population of children, unintentional injuries and homicide are the main causes of death, where the lack of time or the context may preclude the inclusion of palliative care (2). The next largest grouping of illnesses resulting in childhood death is cancer (2), followed by a myriad of diverse conditions. There is a paucity of data in the literature about the main symptoms experienced by children whose deaths are disease related.

In a United States-based study (3) of children who died of cancer, the four main symptoms reported in the last month of life were fatigue, pain, dyspnea and poor appetite. Of more than 80% of the children having pain, relief was achieved in only 27% of the cases. A similar study from Australia (1) examined symptom prevalence and characteristics in 30 inpatients whose deaths were predominantly secondary to cancer. The incidence of pain was noted to be 53% in the last week of life and 31% on the last day of life. Cancer-related symptomatology in 28 children at the end of life in Japan showed that 75% of them had pain during their last weeks of life (4). More recently, a study (5) of 185 children and adolescents receiving palliative care for progressive malignant disease in the United Kingdom showed that pain was a problem for 91.5% of the patients, being highest in patients with solid tumours (if not of the central nervous system). These results were mirrored in a Swedish study (6) with a similar patient population. The scant data on symptom prevalence and adequacy of treatment efficacy in children facing end of life exacerbate the cycle of inadequate treatment.

CASE PRESENTATION

Jenica (Figures 1A, 1B and 1C) was four weeks old when she was diagnosed with acute myelocytic leukemia. Jenica represents a significant population of children in whom pain is a predominant feature of their illness, yet who are unable to self-report because of age or developmental capacity.

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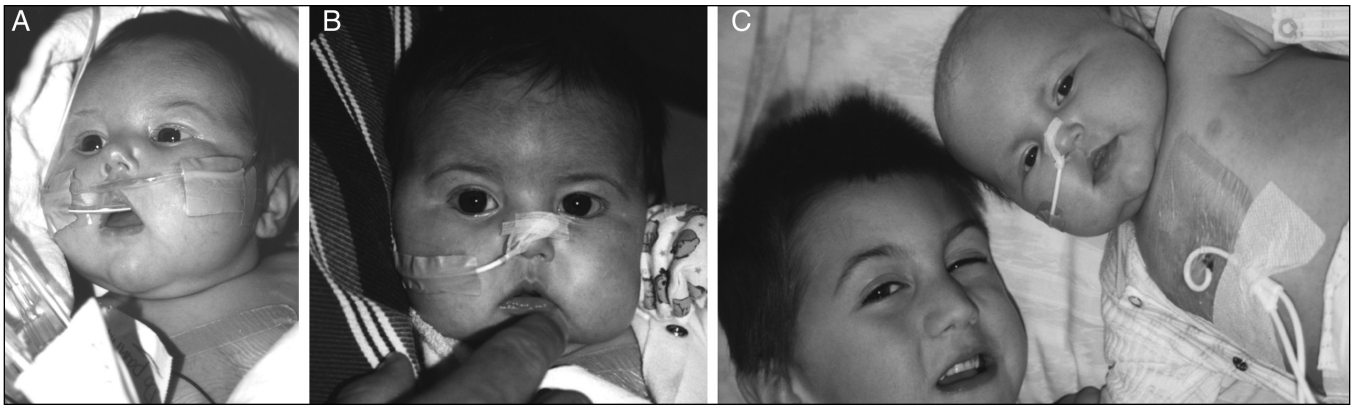

Figure 1) A and **B** *Jenica shortly after diagnosis*. **C** *Jenica did well for nearly one year following her allogenic bone marrow transplant, with her brother (Nicholas) as her donor. However, she then presented at 15 months of age with fever and irritability. She was admitted with a diagnosis of relapse*

Jenica's pain was assessed by behavioural observation by primary caregivers who knew her best and health professionals who came to know her behaviours. During Jenica's early treatment course, she was medicated with parenteral morphine for known painful entities, such as procedures (ie, postoperative central line insertion). Other painful conditions associated with chemotherapy for her leukemia, such as mucositis and typhlitis, were managed with opioid therapy (parenteral morphine) on the basis of general behavioural observations (cry, self-restriction of movements and lack of interest in her environment), and observed response to opioid therapy (more interactive, playful and moving more freely in apparent comfort).

ASSESSMENT

Measuring pain can be a challenge, particularly across the varied developmental capacities inherent in the care of infants, children and adolescents. Many physiological, behavioural and composite scales for the evaluation of pain in children have been introduced over the past 20 years because the usual 'gold standard' of self-report is frequently not an option in pediatrics (7). Although many of these scales were designed for research purposes, without easy applicability to clinical settings, a few scales and tools have proven clinical utility. A complete review of all the available scales is outside the scope of the present article. Readers are referred to the literature (7,8) and to the review written by von Baeyer in this issue of *Pain Research & Management* (9).

Unfortunately, pain is not the sole symptom experienced by children at their end of life. Fatigue, lack of energy, dyspnea, anorexia, nausea and vomiting, insomnia, anxiety and other symptoms are frequently present (1,3,5,6) and negatively influence each other. These symptoms need to be treated as aggressively as pain. They may be difficult to measure, because there is a paucity of pediatric measurement scales for symptoms other than pain. No scales specific to the assessment of pediatric pain and other symptoms at the end of life have been published. The Memorial Symptom Assessment Scale was created to measure multiple symptoms in patients with cancer, and has been validated in children as young as seven years of age (10,11). There are two versions of the scale: one for 10- to 18-year-olds evaluating 30 symptoms, and one for seven- to 12-year-olds evaluating nine symptoms. Similarly, the Douleur Enfant Gustave Roussy behavioural scale can be very useful for young children (two to six years of age). It has been validated in French for use in children with advanced cancer (12).

PAIN MANAGEMENT

Day 1: Jenica initially had good pain relief with resolution of her irritability with 0.5 mg/kg in addition to acetaminophen via her gastrostomy tube every 4 h, around-the-clock.

The importance of ensuring pain relief for the child facing the end of life is a clear medical imperative, hopefully obvious to every clinician. As well, feedback from the child's parents and siblings in several studies (13-16) reinforces the necessity of ensuring excellence in this aspect of care. The possibility of the dying child experiencing pain or other discomfort is a significant concern expressed by parents in numerous studies (13). Ensuring the child's comfort was highlighted by the parents of dying children as being of great value (14,15). Siblings of children with brain tumours expressed how helpful it was to have their sister's or brother's pain treated (16).

Despite its great import, providing such comprehensive care need not be a daunting task. Notwithstanding some unique aspects, pain treatment in the context of pediatric palliative care is not very different from that provided for adults. Two of the first questions to ask the patient and his or her family are: What level of comfort are they aiming for? What are their main goals? (17).

Depending on the primary diagnosis, suffering may have been present for a long time, including chronic pain, with additional acute painful crises or interventions. Some children with life-threatening illnesses continue active, intensive and potentially painful treatments with attendant, potentially painful, side effects. For all patients, pain should be treated and function maximized. One of the easiest and more efficacious treatments is to consider which painful stimuli can be reduced, such as by reviewing the necessity of and/or consolidating various blood tests.

Nonpharmacological measures represent an important part of pain management in pediatric palliative care (18). Integrative methods of pain management encompass methods that integrate physical and psychological approaches and include, for example, hypnosis, relaxation and massage (19). Their goal is to transfer the child's attention from their painful experience to a more pleasant alternative. They can be divided

TABLE 1
Integrative methods of pain management across developmental ages

Age	Physical comforts	Distraction	Cognitive behavioural
Infants: 0 to 1 years	Rocking, swaddling, kangaroo care, pacifier, sucrose, decrease light and noise, massage, Therapeutic Touch	Music, singing, soothing and familiar voice, bubbles, pacifier, mobiles, lullabies and other rhyming patterns	Parent support and guided teaching on how to increase infant's comfort
Preschoolers: 2 to 5 years	Rocking and cuddling, pacifier, sucrose, decreased light and noise, massage, TENS, Therapeutic Touch, positioning for heat/cold packs, acupressure, comfort, physical therapy	Familiar songs, music, pop-up books, puppets, videos, bubble-blowing, stories, stories on tape, clowning, pet visits	Art and music therapy, imagery and hypnosis, therapeutic play, relaxation games (eg, rag doll), participation in favourite stories, simple explanations, parent support and guidance
School-aged: 6 to 11 years	Comfort rocking, cuddling, decrease light and noise, massage, TENS, Therapeutic Touch, positioning for comfort, heat/cold packs, acupressure and acupuncture, physical therapy	Familiar songs, music, pop-up books, puppets, favourite toys and games, videos, bubble-blowing, stories, stories on tape, clowning, pet visits	Art and music therapy, imagery and hypnosis, relaxation games (eg, rag doll, belly breathing), participation in favourite stories, information, biofeedback, psychotherapy, parent support and guidance
Adolescents: 12 to 18 years	Massage, TENS, Therapeutic Touch, positioning for comfort, heat/cold packs, acupressure and acupuncture, physical therapy, adjust environments to teen's preference	Favourite music, games, stories on tape, videos, pet visits, books read aloud	Imagery and hypnosis, art and music therapy, relaxation and deep breathing, information, biofeedback, psychotherapy, parent support and guidance

From reference 19, with permission. TENS Transcutaneous electrical nerve stimulation

into three categories: physical comforts, distraction and cognitive behavioural methods. Like pain measurement tools, they need to be adapted to the child's developmental capacity (Table 1). Complementary and alternative medicine (CAM) can also be used for pain management. There is a plethora of CAM and an overlap between integrative methods and CAM. The major subtypes of CAM are energy therapies, mind-body interventions, biologically based therapies, manipulative and body-based methods, and alternative medical systems (19). There are almost no pediatric studies on the effectiveness of CAM, and experience is mostly anecdotal. At this point, specific evidence-based guidelines are not available, and a careful individual risk-benefit approach is recommended (20).

Pharmacological interventions are often necessary to relieve pain and are best used in combination with nonpharmacological measures. Fifteen years ago, the World Health Organization (WHO) proposed guidelines for a stepwise analgesic approach, matched to pain severity (21,22). The WHO analgesic ladder is also appropriate for use in children and is part of the WHO guidelines for pain and palliative care. Step 1 is for pain that is mild (relieved with acetaminophen or nonsteroidal anti-inflammatory drugs [NSAIDs]). Some now advocate 'skipping' step 2. The rationale is that most patients' pain can be well managed by using steps 1 and 3, without complicating the regimen by using the intermediate step 2, represented by 'weak' opioids used for mild-to-moderate pain (eg, codeine) (23). For pain unrelieved by these first-line agents and for anything other than mild pain, the new approach recommends moving directly to step 3. Step 3 uses opioids without a ceiling effect and typically indicated for moderate-to-severe pain (ie, morphine, hydromorphone and fentanyl). Acetaminophen or NSAIDs can be used at any step of the ladder as adjuvants or co-analgesics (21,22). It is notable that for many children in whom pain may be a prominent feature of their illness, NSAIDs are contraindicated in the setting of renal insufficiency or low platelets, often encountered in the oncological population.

The choice of medication or combination of medications that are best for a specific child is tailored to and influenced by factors such as past medical history, drug allergy or intolerance, preferred route of administration, half-life and availability. Opioids such as morphine, codeine, fentanyl, hydromorphone, oxycodone and methadone can be used safely in children. Early studies (24,25) of opioid use in terminally ill children and youth date back to the 1980s. A recent review (26) detailed the use of opioids for moderate-to-severe pain in pediatric palliative medicine, although the evidence cited remained largely based on studies from a pediatric population not exclusive to end of life. The exception to safe opioid use is meperidine, because the toxic metabolites, specifically normeperidine, accumulate with prolonged use or in the higher dose range, even in patients without renal or hepatic insufficiency. This can result in central nervous system toxicity, including the possibility of dysphoria, seizures and death. Other exceptions are the mixed opioid agonist-antagonists, such as pentazocine and dezocine, which are precluded by their central nervous system toxicity, and psychomimetic and ceiling effects. They can also precipitate a noxious withdrawal event in the opioid-tolerant patient (27). Generally, the children seen for pain management at the end of life are opioid tolerant.

When children at the end of life are unable to take oral medications, there are drugs available in parenteral, transdermal, sublingual or oral transmucosal preparations. Rectally administered preparations are poorly tolerated for repeated dosing and are precluded in the neutropenic and/or thrombocytopenic patient. The nasal/nebulized route has also been tried for opioids, but the mode of administration may be noxious to children. Many of the children with advanced illness have a gastrostomy tube, as did Jenica, and this facilitates options for routes of medication administration.

A newer delivery modality for pain relief, the transdermal route, has been used most commonly for fentanyl. Recent studies (28,29) have documented the efficacy, side effect profile and satisfaction with this delivery system in the pediatric palliative care population in children as young as three years of age. A recent trial (30) has also shown good efficacy and safety in children as young as two years of age with moderate-to-severe chronic pain due to malignant or nonmalignant conditions. It is important to keep in mind that pain with advanced illness and at the end of life can be very dynamic, requiring frequent and aggressive titration. In such instances, the transdermal route is suboptimal because the time to reach steady-state takes longer than dictated by the child's need for immediate pain relief. To be able to perform a successful switch from an oral to a transdermal opioid, the daily dose needed for adequate pain control needs to be stable; this is rarely the case in the context of end of life.

If unable to use the enteral route or when rapid relief or aggressive titration is needed, the parenteral route is the most appropriate. Many children with advanced or chronic illnesses have a central line in situ. When there is no intravenous access, the subcutaneous route is a viable option, via a small gauge indwelling plastic cannula or butterfly needle, obviating the need for repeated injections. Appropriate topical analgesia is required for accessing the portacath or before insertion of the peripheral cannula.

When swallowing represents a difficulty for the patient, the sublingual and oral transmucosal routes can be tried. Although there is a paucity of pharmacological data on opioid metabolism in children using these routes of administration, at least two studies (31,32) have shown promising data on morphine and oxycodone. However, both studies were assessing opioid effect immediately postoperatively, and not in the context of end-of-life care. Oral transmucosal fentanyl, with its rapid onset of action and a short half-life, is also available for breakthrough pain (33,34). This medication may have an important role for acute procedural pain, such as that experienced during dressing changes (35), which may present in debilitated end-stage patients.

More invasive routes, such as the placement of epidural or subarachnoid catheters, are used infrequently in this patient population. The option may be unhelpful because of the pain distribution, which, with advanced disease, is frequently in multiple sites. When the regional approach is considered, the patient's overall medical status may preclude use of this route because of infection or thrombocytopenia. A lack of competent practitioners or comprehensive home care may also figure in the decisions about the analgesic options chosen at end of life. Another important factor is the estimated proximity to death. It may be more appropriate to use systemic agents for pain relief and sedation until death than to subject the child to an intervention in the hours to days leading up to death. A study (36) of children with end-stage cancer and pain localized to one area on their body, in a location where regional interventions were available, noted three main circumstances where these techniques were used: when systemic opioids produced prohibitive side effects; for neuropathic pain unresponsive to appropriate and aggressive systemic opioid titration; and for thoracenteses. This aspect of analgesic care is best provided by skilled and experienced clinicians because an important skill is anticipating and managing the possibility of sudden pain relief in the patient. Such patients are generally profoundly opioid tolerant and the consequent apparent de novo opioid-naïve responses accompanying the new and rapid onset of pain relief must be managed in a comprehensive and proactive manner.

For oncology patients, palliative chemotherapy or radiotherapy can sometimes have a significant role in pain relief. Considerations for radiotherapy include the cancer's radiosensitivity, areas of involvement and possible adverse effects. Another consideration is the capacity to fractionate treatments, to increase the tolerability of the regimen, minimize side effects and balance the length of time (life remaining) tied up in receiving radiotherapy.

There are many options for choosing the dose or the interval of analgesics. Some rules, however, always apply. The medication schedule should meet the patient and his or her family's goals. Generally, unless the pain is very acute and unpredictable, around-the-clock medication should be used to prevent the pain from recurring, rather than 'catching-up' or 'chasing after' pain control, referred to as 'pro re nata' (PRN) dosing. Therefore, when pain occurs at any greater frequency than rare and intermittent, a continuous infusion or similar continuous schedule of analgesic delivery will generally better control the pain compared with intermittent dosing.

Sustained-release medications can be very helpful in decreasing the frequency of medications required, facilitating sleep at night. Once the daily opioid requirement is known and stable for a couple of days, the transition can be made from the immediate- to the sustained-release opioid. With the goal of avoiding 'catch-up', doses for breakthrough pain should be easily available to the child. For enteral medication, 10% of the total opioid dose required over a 24 h period can be given for each breakthrough, every hour, as needed.

When a continuous infusion is used, either delivered via a conventional infusion pump or via a patient-controlled analgesia (PCA) pump, the same estimate to calculate the breakthrough dose can be used. Alternatively, 50% to 200% of the hourly rate is available at least hourly and given as a bolus. When pain is continuous or chronic, especially when the cause of the pain will not resolve, a robust continuous or basal dose of opioid with less frequent, higher boluses ensures more consistent comfort (37). This is a totally different situation than the use of opioid infusions with breakthroughs for postoperative pain, where pain is resolving and the patient is generally opioid naïve (38). In the postoperative situation, the basal rate tends to be nil or small with the provision of small, frequent doses for breakthrough pain.

PCA can offer freedom and flexibility to patients either at the hospital or at home, using a portable pump. In general, the majority of children five to six years of age and older can successfully use a PCA (27). Although there is support for the practice of nurse-controlled analgesia, there is some concern expressed about the use of parent-controlled analgesia in pediatrics (39,40). However, in an end-of-life situation, a child may be too weak or too sick to activate the pump. If he or she is showing signs of apparent pain, it is appropriate for parents or caregivers to activate the PCA pump for the child and relieve the pain. It is important to proactively and pre-emptively discuss with parents, caregivers and staff any of their potential concerns about activating the pump dose button on the child's behalf. Monitoring the child for pain, pain relief and potential adverse effects is a continued responsibility regardless of who is activating the PCA dose button or if providing breakthrough doses by more conventional methods.

Adjuvant medications can also be used in combination with opioids, either functioning as co-analgesics or assisting in decreasing opioid-related side effects. Reliance has been on the adult palliative care and chronic pain literature because there has been no trial of any of the typical adjuvants used in the context of pediatric palliative care. The following principles apply to the use of adjuvant medication (41): balancing the expected positive effects versus potential side effects; ensuring a good understanding of the patient and/or family about what will or could happen; preventing side effects by starting at a low dose and increasing carefully; increasing the dose to optimal effect without intolerable side effects; and providing adequate time for each medication trial.

Neuropathic pain is one of the most frequent indications for adjuvant medication use in pediatric palliative care. Three categories of medication have shown analgesic efficacy (41): anticonvulsants (ie, gabapentin and carbamazepine), tricyclic antidepressants (ie, amitriptyline) and N-methyl-D-aspartate antagonists (ie, ketamine). Of these, gabapentin and amitriptyline are the most often used, with gabapentin having fewer potential side effects. At the lower doses of amitriptyline used for pain control, the side effects are less problematic than experienced with the typically higher doses used for the treatment of depression. As part of the side effect profile, amitriptyline's sedative effect may be beneficial when insomnia is an issue.

When muscle or bone pain is present, conventional NSAIDs can be helpful, although their use is often precluded by such conditions as thrombocytopenia. For their anti-inflammatory effects, selective cyclooxygenase-2 inhibitors such as celecoxib still represent an option in pediatrics, despite the withdrawal of rofecoxib and valdecoxib from the market. Corticosteroids, such as dexamethasone, can reduce inflammatory pain. They have multiple side effects, although these tend to occur with more protracted use. Corticosteroids can provide dramatic pain relief during a pain crisis, especially when associated with compression of the central nervous system or in the setting of increased intracranial pressure. In end-of-life care, steroids as adjuvants can be particularly helpful in contributing to quality of life, through the combination of pain relief, increased appetite and their antiemetic properties.

The choice of adjuvant will be dictated by the individual patient, the circumstances of their illness and how it impacts their pain experience. For example, an infant with painful spasticity and seizures would have a different approach for adjuvant analgesia than an oncology patient with extensive bone metastases.

ADVERSE EFFECTS

Day 3: Two days after her admission, Jenica was less comfortable. Her codeine was increased to 1 mg/kg. This resulted in pruritus, which was relieved by diphenhydramine.

Days 3 and 4: The pruritus was poorly relieved with diphenhydramine. Jenica had less adequate pain relief, crying with diaper changes. The codeine was changed to morphine.

Day 5: Jenica developed marked itching with morphine and the medication was changed to hydromorphone infusion with breakthroughs. Jenica's moaning resolved and she had a transient decrease in her itching. However, her itch worsened over the course of the day despite hydroxyzine and ondansetron. A trial of low-dose naloxone, ranitidine and a tricyclic antidepressant were started, all without relief of pruritus.

Pain medication, including opioids, can have associated adverse effects. Anticipation and prevention of unwanted side effects is key to optimal analgesic therapy. A good bowel regimen, initiated concurrently with opioid therapy, can prevent and treat constipation. Oral naloxone has been used, at a 'usual' starting dose of 0.4 mg given orally, making use of the principle of local opioid receptor action with low bioavailability and, consequently, lack of a systemic effect. The hypothesis is that naloxone inhibits the excitatory G protein opioid receptor, leaving the inhibitory opioid receptor available for pain treatment. A narrow therapeutic index with the potential for analgesia reversal and withdrawal symptoms advise judicious use for the oral route (42,43). Parenteral naloxone should not be used in the opioid-tolerant individual because infinitesimally small amounts of naloxone can dramatically and dangerously reverse analgesia. New peripherally restricted μ-receptor antagonists, such as methylnaltrexone and alvimopan, have the capacity to normalize bowel function without reversing analgesia (43), but are not yet approved for pediatric use.

Opioid-induced pruritus can be a difficult side effect to treat, as evident from Jenica's case description. Animal studies (44,45) suggest that it is mediated by μ-opioid receptors, not histamine receptors. However, antihistamines like diphenhydramine and hydroxyzine can be trialed as a first step. A switch in opioids, such as changing from morphine to hydromorphone, makes use of the principle of incomplete cross-tolerance between the opioids and variability among the opioids and individuals. Changing to another opioid presents a viable option for relief from opioid-induced adverse effects, resulting in less opioid than that calculated by equianalgesic tables. The outcome is an enhanced ratio between analgesia and side effects. This was documented by an Australian study (46) in pediatric cancer patients, in which 90% of children who had their opioids rotated because of side effects or inadequate analgesia had resolution of the side effects. The addition of an adjuvant medication may also help by decreasing the amount of opioid necessary to control the pain.

Nausea may be disease, treatment or opioid related, and can occur with many other medications. The first line of treatment is regular antiemetic medications such as dimenhydrinate or a serotonin 5-hydroxytriptamine-3 receptor antagonist such as ondansetron. When nausea and/or vomiting are a consequence of delayed gastric emptying, prokinetic agents (such as metoclopramide or domperidone) are the treatments of choice. However, their side effects, such as extrapyramidal symptoms, can limit their use. Transdermal scopolamine can be used when position changes or movement triggers the nausea. Modifying the schedule of the opioid or switching to an alternate opioid can also resolve the problem, even when the cause of the nausea is multifactorial. Methotrimeprazine, a neuroleptic, had a long history for its use as an antiemetic for chemotherapy-induced nausea and vomiting before the development of 5-hydroxytriptamine-3 receptor antagonists. Older versions of synthetic cannabis derivatives (ie, nabilone) have been tried. The newer group of agents, including the synthetic cannabinoids, may have an increasingly important role in the treatment of nausea and vomiting, but the evidence is currently insufficient to heartily recommend their use (47). Nonpharmacological therapies, such as

acupuncture, acupressure and hypnosis, may have a role in nausea management (48).

Should sedation and dizziness present with the initiation of opioid therapy, they usually resolve spontaneously within a few days. Sedation may initially be a welcome side effect if the patient has been sleep deprived because of pain. Antipsychotics can be trialed for agitation, confusion or hallucinations, along with reassurance and a calm environment. However, because these adverse effects are so disturbing, a switch to an alternate opioid is usually required. Benzodiazepines may be associated with paradoxical agitation, so a cautious approach to anxiolysis with these agents is prudent while transitioning from one opioid to another. If facing end of life within hours to days, providing sedation rather than changing the opioid is more appropriate.

OPIOID DOSES AT THE END OF LIFE

Clinicians providing pain management for children at the end of life have reported it helpful and reassuring to know what kind of doses have been required and tolerated (49).

The following studies and case reports provide this kind of reassuring information to clinicians. A United States-based study (50) of 53 children dying in a pediatric intensive care unit examined analgesic and sedative use. Eighty-nine per cent of the children were treated with opioids, sedatives or both during withdrawal of their potentially life-sustaining treatments. The documented doubling of the mean dose of their baseline opioid is consistent with emerging recommendations for ensuring comfort at end of life in the context of forgoing life-sustaining interventions in the intensive care unit (51). A classic report from the late 1990s (52) reviewed opioid use in 121 neonates for whom life support was being discontinued. Results showed that 84% of patients were treated with opioids at the time of discontinuation of assisted ventilation. The majority were treated with doses of 0.1 mg/kg to 0.2 mg/kg of parenteral morphine whereas those infants who were opioid tolerant received 1 mg/kg. Also of significance was the complete lack of relationship between opioid dosing and survival.

An Australian study (1) of 30 children in their last week of life with an average age of 8.9 years reported that the majority were treated with opioids (95%). The mean opioid dose, expressed as parenteral morphine equivalents (PMEs), was 0.08 mg/kg/h (range 0.01 mg/kg/h to 1 mg/kg/h). Considering that the typical postoperative PME dose for major abdominal surgery is 0.02 mg/kg/h to 0.04 mg/kg/h, the mean dose used in this pediatric population at end of life was two- to fourfold the usual postoperative dose (range comparable with 0.5 to 30 times the 'usual' postoperative dosing). Similarly, a Finnish study (53) of children dying from cancer showed that opioid use approached 100-fold of what is typically required in the postoperative period, with a range of 0.007 mg/kg/h to 2.3 mg/kg/h of PMEs.

The only free-standing children's hospice in Canada, at the time of their 1995-2001 review, recorded opioid use at the end of life in 42 children (54). The median dose of 0.085 mg/kg/h PME was comparable with other studies cited, being two- to fourfold the 'usual' postoperative dosing. Impressively, 50% of these children required 200 to 3000 times the 'usual' postoperative dose range, with their mean documented parenteral morphine dose of 4.86 mg/kg/h to 73.9 mg/kg/h. Remarkable dose ranges of opioids required at end of life in the pediatric population were similarly documented (55), with extraordinary doses of 3.8 mg/kg/h to 518 mg/kg/h PMEs being required for six to 240 days. Isolated case reports (49) of children at end of life noted 150 mg/kg/h PMEs in children.

A remarkable case report (56) detailed the doses of morphine used in a four-month-old, 5.4 kg infant with rhabdoid cancer. At 2680 mg/h of intravenous morphine, this infant required 150,000 times the 'usual' postoperative dose, which would compare with an equivalent dose of 30,000 mg/h for a 60 kg adult. Notable is the dose titration chart, which shows the dramatic opioid escalation with the clear temporal relationship showing that despite the magnitude of the dosing increments, this did not hasten the infant's death (Figure 2). Respiratory depression is virtually nonexistent in the opioid-tolerant patient unless the pain stimulus is suddenly removed, as in a successful regional or neurolytic block.

With these reports of the kinds of opioid doses that have been used in the management of pain in children at end of life, it is very important to clarify that these doses truly are extraordinary. Generally, 'conventional' analgesic doses and routes are effective for the vast majority of children at end of life. This has been well documented in a retrospective chart review of 199 children and young adults, in which only 6% required 'massive' opioid doses (100 times the 'usual' postoperative dosing). An even smaller subset of this group required 'extraordinary' measures, such as sedation or subarachnoid opioid infusions (36,55).

Should clinicians find themselves trying to manage pain that is out of the conventional range they are most familiar with, consultation with local or distant resources with additional expertise and experience is a necessary part of their management of the child's pain. Pediatric palliative care and pain management services are able to be contacted, and can help strategize alongside the child's treating clinicians. Sometimes, it is important to review what has been trialed to date to reassure the clinician and family that all possible measures have been taken, particularly before embarking on sedation at the end of life when pain or other symptoms have been deemed 'intractable'.

The concept of not reserving analgesia for end of life is a moral and ethical imperative, obligating clinicians to provide appropriate analgesia at any point in the course of the child's illness. Illustrative of palliation provided concurrently with cure-oriented goals of care is the study of pain and symptom management in children and young adults with cystic fibrosis (57). In their last 12 h of life, antibiotic therapy was continued for 75% of patients, 72% continued oral preventive and therapeutic medications and 36% had chest physiotherapy. While several of these patients were listed for transplant, all patients also had their goals of care addressed with the clarification that resuscitative interventions would not be pursued. Eighty-six per cent of these patients were concurrently receiving opioids for breathlessness and pain.

For the vast majority of patients, excellent pain relief while maximizing function is achievable. On occasion, in the setting of intractable pain or another distressing symptom such as breathlessness, it may not be possible to provide adequate relief without compromise of the sensorium. The addition of sedation to the analgesia may be required if all other options have been explored in a timely fashion by those with palliative medicine expertise.

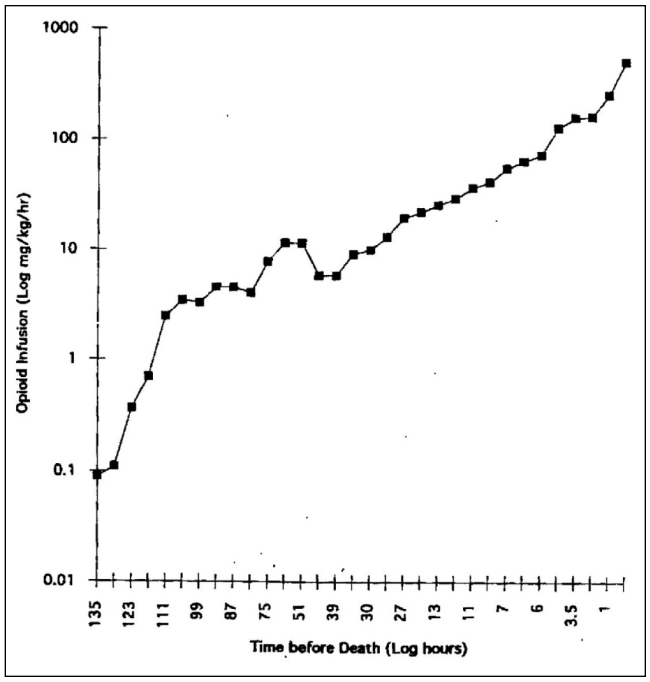

Figure 2) *Graph indicating escalation in opioid infusion in a four-month-old, 5.4 kg infant days before death. Figure from reference 56 with permission*

Day 6: Jenica was given lorazepam, with transient settling. As her disease progressed, she had significant cardiorespiratory decompensation with increased respiratory effort, central cyanosis and hypoxemia.

Despite obvious clinical deterioration and fluctuating level of consciousness, Jenica continued to scratch at her face and abdomen. She settled with regularly scheduled lorazepam and the addition of methotrimeprazine and hydromorphone infusions with breakthroughs.

Day 7: The hydromorphone was changed to fentanyl with the goal of possibly decreasing Jenica's pruritus, affording decreased sedation with increased function. However, it was soon realized that increased function was not possible and so the plan of care changed to keep Jenica sedated until her death.

Day 12: Jenica died in apparent comfort on fentanyl 2.5 µg/kg/h with breakthroughs, methotrimeprazine 0.5 mg/kg/h with breakthroughs, lorazepam 0.05 mg/kg every 6 h, diphenhydramine 1 mg/kg every 6 h, acetaminophen 10 mg/kg every 4 h and an anticholinergic for secretions.

BARRIERS TO ADEQUATE PAIN CONTROL IN PEDIATRIC PALLIATIVE CARE

Multiple obstacles can block the road to pain relief for children (17,58-62). The recognition of those fears and barriers is essential. Education of both health care professionals and of patients and their families will help the understanding and acceptance of pain treatment. The main barriers are listed in Table 2.

TABLE 2
Barriers to adequate pain control

Nonrecognition of the pain, including denial of its presence
Nonrecognition of the global nature of pain, including psychological, social and cultural aspects
Fear of doing harm and of side effects
Fear of addiction and abuse
Fear of diverted use
Physician hubris: when a physician chooses not to ask for assistance from pain specialists
Exclusion of concurrent nonpharmacological measures
Denial by parents, causally linking pain as a sign of deterioration
Patients' and parents' impression that the pain must be unable to be relieved, otherwise it would be addressed by the medical team

WHAT'S ON THE HORIZON?

Recent advances in the development of new pain treatments have led to the marketing of new medications or of more convenient delivery systems. Depending on the country, availability or approval may be limited, especially for patients younger than 18 years of age. Cannabis-based medicines are among the new classes of medication. A combination of delta-9-tetrahydrocannabinol and cannabidiol (63,64) has recently been released to treat neuropathic pain in multiple sclerosis, and additional neuropathic pain trials are being conducted. As cancer pain is better understood (65), new medications are being developed to more specifically target the receptors located on nociceptors; osteoprotegerins, for bone cancer pain; and TRV1 antagonists, for acid-producing cancers (66). The availability of less invasive delivery systems will also be welcome. Nasal spray, as in cannabis-based medications such as delta-9-tetrahydrocannabinol and cannabidiol combined (63,64), can be used even in a child who is unable to eat or swallow. A novel type of patient-controlled transdermal patch, using iontophoresis for breakthrough pain, will allow the patient to receive bolus doses of fentanyl over 10 min, without the need for pumps, tubing and venous access. This technique has been shown to be equivalent to the use of a standard postoperative PCA in the adult setting (67). Other transdermal medications are in development, using different physical enhancement mechanisms to help larger molecules cross the skin barrier.

Unfortunately, in the pharmaceutical world, the 'pediatric gap' still exists (68). The vast majority of the drugs used to treat pain, especially for adjuvants, are still used 'off-label' in pediatric patients. The Food and Drug Administration Modernization Act (69) improved the situation by stimulating pediatric clinical studies, but very few pain medications were included. The inclusion of children in clinical trials for existing and new pain medications is necessary to ensure safe use of these medications in the pediatric population.

More research is also needed in pediatric palliative care to improve pain and other symptom management. Although there are many obvious methodological challenges to research in this context, we recently observed a net increase in the number of research articles published. An informal MEDLINE search using the term "pediatric palliative care" revealed 300 papers between 1996 and 2006, compared with 71 papers between 1985 and 1995. A recent review (70) has highlighted the challenges of research in pediatric palliative care, supported by suggestions for overcoming barriers through the use of creative and flexible methodological designs.

CONCLUSIONS

Excellent pain control can drastically improve the quality of life for children with life-threatening conditions. A multidisciplinary team with an open attitude to differences, listening skills, availability, flexibility, creativity, resourcefulness and empathy can help the child and his or her family to live with the least pain possible. Planning for what could happen is often the key to excellence in pediatric palliative care. Honest and dynamic discussion about the goals of treatment, the possible options, and their respective side effects provides support to the patient and his or her family to make choices that best fit with their wishes. The respect for the dignity of the patient and of his or her family and the reassurance that they are not alone in such difficult times will help lessen their collective suffering.

ACKNOWLEDGEMENTS: We express our thanks to the family of Jenica Saulnier who so generously have agreed to share her story and picture so that others can learn from her life. Marie-Claude Grégoire is supported by the IWK Board of Directors, and the Canadian Institutes of Health Research.

REFERENCES

1. Drake R, Frost J, Collins JJ. The symptoms of dying children. J Pain Symptom Manage 2003;26:594-603.
2. Martin JA, Kochanek KD, Strobino DM, Guyer B, MacDorman MF. Annual summary of vital statistics – 2003. Pediatrics 2005;115:619-34.
3. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med 2000;342:326-33.
4. Hongo T, Watanabe C, Okada S, et al. Analysis of the circumstances at the end of life in children with cancer: Symptoms, suffering and acceptance. Pediatr Int 2003;45:60-4.
5. Goldman A, Hewitt M, Collins GS, Childs M, Hain R; United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses' Forum Palliative Care Working Group. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum Survey. Pediatrics 2006;117:e1179-86.
6. Jalmsell L, Kreicberg U, Onelov E, Steineck G, Henter JI. Symptoms affecting children with malignancies during the last month of life: A nationwide follow-up. Pediatrics 2006;117:1314-20.
7. Finley GA, McGrath PJ, eds. Measurement of Pain in Infants and Children. Seattle: IASP Press, 1998.
8. Franck LS, Greenberg CS, Stevens B. Pain assessment in infants and children. Pediatr Clin North Am 2000;47:487-512.
9. Von Baeyer C. Children's self-reports of pain intensity: Scale selection, limitations, and interpretation. Pain Res Manag 2006;11:157-62.
10. Collins JJ, Byrnes ME, Dunkel IJ, et al. The measurement of symptoms in children with cancer. J Pain Symptom Manage 2000;19:363-77.
11. Collins JJ, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: The validation of the Memorial Symptom Assessment Scale in children aged 7-12. J Pain Symptom Manage 2002;23:10-6.
12. Gauvain-Piquard A, Rodary C, Rezvani A, Serbouti S. The development of the DEGR(R): A scale to assess pain in young children with cancer. Eur J Pain 1999;3:165-76.
13. Widger KA, Wilkins K. What are the key components of quality perinatal and pediatric end-of-life care? A literature review. J Palliat Care 2004;20:105-12.
14. Contro N, Larson J, Scofield S, Sourkes B, Cohen H. Family perspectives on the quality of pediatric palliative care. Arch Pediatr Adolesc Med 2002;156:14-9.
15. Mack JW, Hilden JM, Watterson J, et al. Parent and physician perspectives on quality of care at the end of life in children with cancer. J Clin Oncol 2005;23:9155-61.
16. Freeman K, O'Dell C, Meola C. Childhood brain tumors: Children's and siblings concerns regarding the diagnosis and phase of illness. J Pediatr Oncol Nurs 2003;20:133-40.
17. Galloway KS, Yaster M. Pain and symptom control in terminally ill children. Pediatr Clin North Am 2000;47:711-46.
18. Goldman A, Frager G, Pomietto M. Pain and palliative care. In: Schechter NL, Berde CB, Yaster M, eds. Pain in Infants, Children, and Adolescents, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2003:539-62.
19. Kuttner L. Pain – an integrative approach. In: Goldman A, Hain R, Liben S, eds. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press, 2006:332-341.
20. Scrace J. Complementary therapies in palliative care of children with cancer: A literature review. Paediatr Nurs 2003;15:36-9.
21. WHO Ladder: Cancer Pain Relief and Palliative Care. Technical Report Series 804. Geneva: World Health Organization, 1990.
22. World Health Organization. Cancer Pain Relief and Palliative Care in Children. Geneva, Switzerland: World Health Organization, 1998.
23. Maltoni M, Scarpi E, Modonesi C, et al. A validation study of the WHO analgesic ladder: A two-step vs three-step strategy. Support Care Cancer 2005;13:888-894.
24. Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. J Pediatr 1980;96:930-2.
25. Miser AW, Davis DM, Hughes CS, Mulne AF, Miser JS. Continuous subcutaneous infusion of morphine in children with cancer. Am J Dis Child 1983;137:383-5.
26. Hain RD, Miser A, Devins M, Wallace WH. Strong opioids in pediatric palliative medicine. Paediatr Drugs 2005;7:1-9.
27. Yaster M, Kost-Byerly S, Maxwell LG. Opioid agonists and antagonists. In: Schechter NL, Berde CB, Yaster M, eds. Pain in Infants, Children, and Adolescents, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2003:181-224.
28. Noyes M, Irving H. The use of transdermal fentanyl in pediatric oncology palliative care. Am J Hosp Palliat Care 2001;18:411-6.
29. Hunt A, Goldman A, Devine T, et al. Transdermal fentanyl for pain relief in a paediatric palliative care population. Palliat Med 2001;15:405-412.
30. Finkel JC, Finley GA, Greco C, Weisman SJ, Zeltzer L. Transdermal fentanyl in the management of children with chronic severe pain. Cancer 2005;104:2847-57.
31. Kokki H, Rasanen I, Lasalmi M, et al. Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. Clin Pharmacokinet 2006;45:745-54.
32. Engelhardt T, Crawford M. Sublingual morphine may be a suitable alternative for pain control in children in the postoperative period. Paediatr Anaesth 2001;11:81-3.
33. Mystakidou K, Katsouda E, Parpa E, Vlahos L, Tsiatas ML. Oral transmucosal fentanyl citrate: Overview of pharmacological and clinical characteristics. Drug Deliv 2006;13:269-76.
34. Aronoff GM, Brennan MJ, Pritchard DD, Ginsberg B. Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. Pain Med 2005;6:305-14.
35. Roberts R, Brack A, Blakeney P. A double-blind study of the analgesic efficacy of oral transmucosal fentanyl citrate and oral morphine in pediatric patients undergoing burn dressing change and tubbing. J Burn Care Rehabil 2003;24:351-5.
36. Collins JJ, Grier HE, Sethna NF, et al. Regional anesthesia for pain associated with terminal pediatric malignancy. Pain 1996;65:63-9.
37. Cherney NJ, Foley KM. Nonopioid and opioid analgesic pharmacotherapy of cancer pain. Hematol Oncol Clin North Am 1996;10:79-102.
38. Frager G. Pediatric Palliative care. In: Joishy SK, ed. Palliative Medicine Secrets. Philadelphia: Hanley & Belfus, Inc, 1999:157-73.
39. Monitto CL, Greenberg RS, Kost-Byerly S, et al. The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. Anesth Analg 2000;91:573-9.
40. Berde CB, Solodiuk J. Multidisciplinary programs for management of acute and chronic pain in children. In: Schechter NL, Berde CB, Yaster M, eds. Pain in Infants, Children, and Adolescents, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2003:471-86.
41. Drake R, Hain R. Pain – Pharmacological management. In: Goldman A, Hain R, Liben S, eds. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press, 2006:304-31.

42. Meissner W, Schmidt U, Hartmann M, et al. Oral naloxone reverses opioid-associated constipation. Pain 2000:84:105-9.
43. Kurz A, Sessler DI. Opioid-induced bowel dysfunction. Drugs 2003;63:649-71.
44. Kuraishi Y, Yamaguchi T, Miyamoto T. Itch-scratch responses induced by opioids through central mu opioid receptors in mice. J Biomed Sci 2000;7:248-52.
45. Ko MC, Song MS, Edwards T, et al. The role of central mu opioid receptors in opioid-induced itch in primates. J Pharmacol Exp Ther 2004;310:169-76.
46. Drake R, Longworth J, Collins JJ. Opioid rotation in children with cancer. J Palliat Med 2004;7:419-21.
47. Glare P, Pereira G, Kristjanson LJ, Stockler M, Tattersall M. Systematic review of the efficacy of antiemetics in the treatment if nausea in patients with far-advanced cancer. Support Care Cancer 2004;12:432-40.
48. Vickers AJ, Cassileth BR. Unconventional therapies for cancer and cancer-related symptoms. Lancet Oncol 2001;2:226-32.
49. Jones PD, Wilkinson IA. Massive opioid requirements in children with disseminated central nervous system disease. J Pediatr 1996;128:864-5.
50. Burns JP, Mitchell C, Outwater KM, et al. End-of-life care in the pediatric intensive unit after the forgoing of life-sustaining treatment. Crit Care Med 2000;28:3060-6.
51. Truog RD, Cist AF, Brackett SE, et al. Recommendations for end-of-life care in the intensive care unit: The Ethics Committee of the Study of Critical Care Medicine. Crit Care Med 2001;29:2332-48.
52. Partridge JC, Wall SN. Analgesia for dying infants whose life support is withdrawn or withheld. Pediatrics 1997;99:76-9.
53. Sirkia K, Hovi L, Pouttu J, Saarinen-Pihkala UM. Pain medication during terminal care of children with cancer. J Pain Symptom Manage 1998;15:220-6.
54. Siden H, Nalewajek. High dose opioids in pediatric palliative care. J Pain Symptom Manage 2003;25:397-9.
55. Collins JJ, Grier HE, Kinney HC, Berde CB. Control of severe pain in children with terminal malignancy. J Pediatr 1995;126:653-7.
56. Collins JJ, Berde CB, Grier HE, et al. Massive opioid resistance in an infant with localized metastasis to the midbrain periaqueductal gray. Pain 1995;63:271-5.
57. Robinson WM, Ravilly S, Berde C, Wohl ME. End-of-life care in cystic fibrosis. Pediatrics 1997;100:205-9.
58. McGrath PA. Pain control. In: Doyle D, Hanks GWC, MacDonald N, eds. Oxford Texbook of Palliative Medicine, 2nd edn. New York: Oxford University Press, 1998:1013-31.
59. Liben S. Pediatric palliative medicine: Obstacles to overcome. J Palliat Care 1996;12:24-8.
60. Liben S, Goldman A. Home care for children with life-threatening illness. J Palliat Care 1998;14:33-38.
61. McGrath PJ, Finley GA. Attitudes and beliefs about medication and pain management in children. J Palliat Care 1996;12:46-50.
62. Chaffee S. Pediatric palliative care. Prim Care 2001;28:365-90.
63. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief if central neuropathic pain from brachial plexus avulsion: Results of a randomized controlled trial. Pain 2004;112:299-306.
64. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. Anaesthesia 2004;59:440-52.
65. Luger NM, Mach DB, Sevcik MA, Mantyh PW. Bone cancer pain: From model to mechanism to therapy. J Pain Symptom Manage 2005;29(Suppl 5):S32-S46.
66. Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. Nat Rev Cancer 2002;2:201-9.
67. Viscusi ER, Reynolds L, Chung F, Atkinson LE, Khanna S. Patient-controlled transdermal fentanyl hydrochloride vs intravenous morphine pump for postoperative pain: A randomized controlled trial. JAMA 2004;291:1333-41.
68. Groopman J. The Pediatric Gap. The New Yorker, January 10, 2005.
69. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. JAMA 2003;290:905-11
70. Graham R, Dussel V, Wolfe J. Research. In: Goldman A, Hain R, Liben S, eds. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press, 2006:613-47.