

9 Paediatric palliative medicine

9.1 Pain control

Patricia A. McGrath and Stephen C. Brown

Introduction

Pain control is an integral component of paediatric palliative care. Children may experience many different types of pain from invasive procedures, the cumulative effects of toxic therapies, progressive disease, or psychological factors. The pain is often complex with multiple sources, comprised of nociceptive and neuropathic components. In addition, several situational factors usually contribute to children's pain, distress, and disability. Thus, to adequately treat pain in children receiving palliative care, we must evaluate the primary pain sources and ascertain which situational factors are relevant for which children and families. Treatment emphasis should shift accordingly from an exclusive disease-centred framework to a more child-centred focus.

In this chapter, we describe a child-centred framework for understanding and controlling pain for children receiving palliative care. Pain control should include regular pain assessments, appropriate analgesics administered at regular dosing intervals, adjunctive drug therapy for symptom and side-effects control, and non-drug interventions to modify the situational factors that can exacerbate pain and suffering. Since much specific information on pain control (presented in Chapter 9.2) is also relevant for children, basic information on pathophysiology, pharmacology, and physical interventions is not repeated in this chapter. Instead, this chapter provides a complementary focus to the other contributions in this textbook by describing the unique nature of children's pain including the primary factors that affect their pain and quality of life, presenting guidelines for selecting and administering drug therapy in accordance with the nociceptive and neuropathic components, and recommending practical non-drug therapies for integration within a hospital, home, or hospice setting.

The nature of children's pain

Throughout the last decade, we have gained an increasing appreciation for the plasticity and complexity of children's pain. As with adults, children's pain is often initiated by tissue damage caused by noxious stimulation, but the consequent pain is neither simply nor directly related to the amount of tissue damage. Perhaps even more than in adults, differing pain responses to the same tissue damage are noted. The eventual pain evoked by a relatively constant noxious stimulus can be different depending on children's expectations, perceived control, or the significance that they attach to the pain.⁽¹⁾ Children do not sustain tissue damage in an isolated manner, devoid of a particular context, but actively interpret the strength and quality of any pain sensations, determine the relevance of any hurting, and learn how to interpret the pain by observing the general environment, especially the behaviour of other people. Children's perceptions of pain is defined by

their age and cognitive level; their previous pain experiences, against which they evaluate each new pain; the relevance of the pain or disease causing pain; their expectations for obtaining eventual recovery and pain relief; and their ability to control the pain themselves. While plasticity and complexity are critical features for all pain perception, plasticity seems an even more important feature for controlling children's pain.

Much research has been conducted to identify the critical factors responsible for the plasticity of pain perception (for review see ref. 2). Animal behaviour studies, in which the physiological responses activated by a noxious stimulus are directly recorded, have demonstrated that certain factors, such as the primate's attention, the predictability of a painful stimulus, and the relevance of the stimulus can directly modify the intensity of the physiological responses evoked by a constant noxious stimulus. Parallel psychophysical studies, in which adults rate the painfulness of constant noxious stimuli in different contexts, have demonstrated that these same factors can modify the perceived intensity and unpleasantness of the consequent pain sensations. Psychologically mediated modulation of pain can occur at the earliest levels of pain processing, but also at the highest levels. Recent PET and functional MRI studies have demonstrated that painful stimulation activates different cortical regions—depending on an individual's expectations and attention.⁽³⁾ Human studies evaluating the impact of environmental and psychological factors on the perception of experimentally induced pain study have been conducted primarily in adults. However, results from the few laboratory studies conducted with children are consistent with those from adult studies.^(4,5) In addition, much compelling evidence about the powerful mediating role of psychological factors in children's pain derives from clinical studies of acute, recurrent, and chronic pain. These studies highlight the need to recognize and evaluate the mediating impact of these factors in order to optimally control children's pain.

The model illustrated in Fig. 1 provides a framework for assessing these factors, based on our knowledge of the plasticity and complexity of children's pain. Some factors are relatively stable for a child, such as gender, temperament, and cultural background while other factors change progressively, such as age, cognitive level, previous pain experience, and family learning (listed in the open box in the figure). These child characteristics shape how children generally interpret and experience the various sensations caused by tissue damage. In contrast, the cognitive, behavioural, and emotional factors (listed in the shaded boxes) are not stable. They represent a unique interaction between the child and the situation in which the pain is experienced.^(1,6) These situational factors can vary dynamically throughout the course of a child's illness, depending on the specific circumstances in which children experience pain. For example, a child receiving treatment for cancer will have repeated injections, portacatheter access, and lumbar punctures—all of which may cause some pain (depending on the analgesics, anaesthetics, or sedatives used). Even though the tissue damage from these procedures is the same each time, the particular set of situational factors for each treatment is unique for a child—depending on a child's (and parent's expectations), a child's (and parent's and staff's behaviours), and on a child's (and family's) emotional state. Although the causal relationship between an injury and a consequent pain seems direct

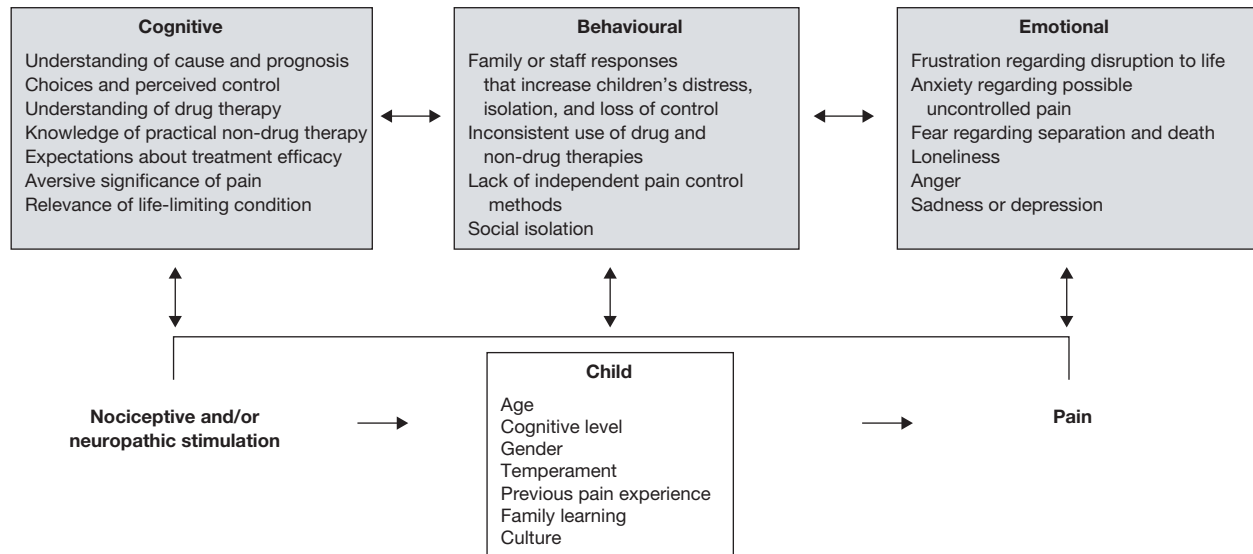


Fig. 1 A model depicting the situational factors that modify children's pain perception.

and obvious, what children understand, what they do, and how they feel all affect their pain. Certain factors can intensify pain, exacerbate suffering, or affect adversely a child's quality of life.⁽⁴⁾ While parents and health care providers may be unable to change the more stable child characteristics, they can modify situational factors and dramatically improve children's pain and lives.

The impact of situational factors on children's pain

Cognitive factors include children's understanding about the pain source, their ability to control what will happen, their expectations regarding the quality and strength of pain sensations that they will experience, their primary focus of attention (that is distracted away from or focused primarily on the pain), and their knowledge of pain control strategies. In general, children's pain can be lessened by providing accurate age-appropriate information about pain, for example emphasizing the specific sensations that children will experience (such as the stinging quality of an injection, rather than the general hurting aspects), by increasing their control and choices, by explaining the rationale for what can be done to reduce pain, and by teaching them some independent pain reducing strategies.^(1,7) For children receiving palliative care, key cognitive factors also include the relevance or meaning of their illness—particularly its life-threatening potential, their beliefs about death and their understanding of the significance of their lives.

Behavioural factors refer to the specific behaviours of children, parents, and staff when children experience pain and also encompass parents' and children's wider behaviours in response to a chronic pain problem or progressive illness. Common behavioural factors include children's distress or coping reactions (e.g. crying, using a pain control strategy, withdrawing from life) and parent's and health staff's subsequent reactions to them (e.g. displaying frustration, calmly providing encouragement for children to use pain control strategies, engaging them in conversation and activities).⁽⁴⁾ They also include the extent to which children are physically restrained during invasive or aversive treatments and the broader physical and social restrictions on children's and family's lives as children become sicker. Distress behaviours and some altered behavioural patterns may initiate, exacerbate, or maintain children's pain. In general, as children's mental or physical activity increases, as children use coping and pain control methods, as their distress and disability behaviours decrease, and as staff and parental responses become more consistent in encouraging them to use pain control

methods, their pain should lessen. Children receiving palliative care seem to report less pain, feel less distressed by pain, and have a higher quality of life when families and staff encourage them to remain engaged in life and live as fully as possible.

Emotional factors include parents' and children's feelings in response to pain, to the daily effects of the underlying illness or condition, and to the subsequent impact of the children's deaths on the family. Children's emotions affect their ability to understand what is happening, their ability to cope positively, their behaviours, and ultimately their pain. Children's immediate emotional reactions to pain may vary from a relatively neutral acceptance to annoyance, anxiety, fear, frustration, anger, or sadness. The specific emotions depend on the nature of the pain—type, cause, intensity, and duration—and its impact on their lives. In general, the more emotionally distressed children are the stronger or more unpleasant their pain. When children do not understand what is happening, when they lack control and do not know independent pain control strategies, their emotional distress increases and their pain intensifies. Similarly, when children's behaviours are restricted, when they are physically restrained during medical procedures, or when their usual daily activities and social interactions are disrupted, their emotional distress and pain can intensify. Children with life-threatening conditions may not understand what they are feeling or may be unable to verbalize their fears and anxieties. Yet, almost all children will become aware of differences in how their parents and families respond to them as they progress from receiving active curative treatments to receiving only palliative therapies. Even very subtle behavioural cues can still evoke fear, uncertainty, apprehension, or depression depending on children's ages and what they understand about death and separation. Thus, an essential component of pain control should be evaluating whether these emotions are exacerbating children's pain and distress and impairing the quality of their lives.

Situational factors in paediatric palliative care

Cognitive and emotional factors are the most salient situational factors that affect pain for children receiving palliative care. Children probably have already endured a prolonged period of intermittent pain, physical disability, and multiple aversive treatments. Children who were receiving curative therapies become more focused on the future consequences of their disease. Their thoughts, behaviours, and feelings change as they begin to

understand that they are dying. Naturally, the type of support, information, and guidance children require also changes. While the impact is profound for all children and families, each child and family is unique with respect to their specific psychological, medical, social, and spiritual needs. All families experience anguish and grief, but they may also experience denial, anxiety, anger, guilt, frustration, and depression. It is essential that health professionals listen attentively and observe carefully not only to ensure that all the needs of both the child and family are met but also to resolve the myriad factors that can exacerbate children's pain and suffering. The primary situational factors in paediatric palliative care are listed in Table 1. This summary has evolved from our treatment of children referred to the pain clinic. Child and family factors are listed in italics; the factors that are relevant for health staff, as well as families, are listed in roman print.

The shift in care from curative to palliative therapies may signify to some children and families that health professionals are giving up on the child. Children and families must understand that stopping ineffective therapies is not giving up, but represents a rational decision based on children's best interests. Pain control is an essential component of palliative care.^(8–14) Children and parents should not fear that health professionals have given up on controlling pain and aversive symptoms. Pain and all symptoms must be treated aggressively from the dual perspective of targeting the primary source of tissue damage and modifying the secondary contributing factors. Although most families receive accurate information about their disease and required treatments, few children or their parents receive

concrete information about their pain, the factors that can attenuate or exacerbate it, a rationale for the interventions they receive, and training in effective non-drug pain control methods. The latter may be particularly important for children in palliative care, who have diminishing control in their lives. Children and their parents often do not understand that pain control therapies may vary in efficacy due to changing disease, the effects of other drugs, and situational factors. Thus, their confidence in certain pain control therapies can decrease, even though these therapies would effectively alleviate pain at another time. The fear of inadequate pain control places an enormous emotional burden on an already distressed child and family and can create a situation in which children's pain and disability intensifies.

Generally, children's physical activity has been progressively restricted due to the disability caused by their condition. Parents who encourage children to adopt passive patient roles, to behave differently than other children, and to depend primarily on others for pain control will undoubtedly create a situation wherein children's pain is maximized. Even when children are somnolent, it is possible to create some 'normal environment' in which children can participate and actively involve themselves during their alert periods. Children should live as fully as possible, even though they are also dying.

Children who experienced adverse physical effects from medication, such as hair loss and weight gain, may have become acutely self-conscious about their appearance. As a result, these children may have progressively withdrawn from social interactions with their peers because they anticipated negative reactions. Children become more distant from the people and activities that they had enjoyed. Moreover, many children may lose the opportunity to be regarded as unique individuals by the friends and classmates they value; instead, they are regarded increasingly as sick, different, or even dying. Their peers and their daily accomplishments (whether social, academic, or athletic) had provided special meaning about children's unique value in the world. While families emphasize children's value to them and to the world, children often lose the objective feedback they routinely received. The increased withdrawal and social isolation can exacerbate their pain and emotional distress. Their withdrawal may increase when treatment emphasis shifts from cure and palliation to palliation alone. Parents may 'close-in', spending even more exclusive time with the dying child as a closed family unit. While important for children and families, the exclusive focus on the family increases a child's social isolation and may cause more anxiety for some children—particularly when the family does not openly address children's concerns about death and dying. Inadvertently, the family may prevent children from interacting both with peers who can lessen their anxiety through play and conversation and also with health professionals who can help them to resolve their anxiety and fears about dying.

Children seem to know intuitively, even when dying has not been discussed directly with them. They fear separation and abandonment; some children may fear that their illness is a punishment. Dying children may feel frightened, isolated, and guilty unless they are able to openly express and resolve their concerns. Many observers have noted that children who are dying have a level of maturity 'far beyond their years'. It is essential to acknowledge and resolve their fears. Children should receive accurate information, consistent with their spiritual beliefs, presented in a calm reassuring manner. They may need concrete reassurance that they will not suffer when they die, that they will not be alone, and that their families will remember them. Unresolved emotions add anguish and may intensify their pain. (For the comprehensive care of the dying child, please see refs 11, 15–19.)

Optimal pain control for children

Pain control is an intrinsic component of paediatric palliative care. Since children may experience complex pains due to myriad physical and psychological factors, pain control must be child-centred rather than disease-centred. Health care providers must carefully evaluate the varied causes and

Table 1 Situational factors in paediatric palliative care

Cognitive factors

Meaning of death

Inaccurate understanding

Impact of situational factors on pain and quality of life

Course of disease

Palliative versus curative therapy

Little independent control over pain

Limited choices

Expectation for continuing pain and suffering

Misunderstanding of drug therapy

Opioids

Dosing and administration

Criteria for evaluating effectiveness

Behavioural factors

Social withdrawal

Physical inactivity

Passive approach to pain control

Secondary gains

Stress reduction

Emotional denial

Parent or staff attention

Inappropriate drug management

Choice or mode of drug administration

Failure to aggressively treat opioid-related side-effects

Failure to evaluate pain sources and document pain level

Failure to use effective non-drug therapies

Emotional

Anxiety about

Dying and death

Suffering

Meaning of life

Fear of

Separation

Inadequate pain control

Increasing adverse symptoms

Impact on family

Anger

Sadness or depression

Distancing by staff and friends

contributing factors to select the most effective therapies for each child's pain.

Onset, location, intensity, quality, duration (or frequency, if recurring), spatial extent, temporal pattern, and accompanying physical symptoms are the key pain characteristics for assessment, as listed in Table 2. All these

Table 2 Primary components of pain assessment

<i>Sensory characteristics</i>	<i>Cognitive factors</i>
Onset	Understanding of pain source
Location	Understanding of diagnosis, treatment, and prognosis
Intensity	Expectations
Quality	Perceived control
Duration	Relevance of disease or painful treatments
Spread to other sites (consistent with neurological pattern)	Knowledge of pain control
Radiation	<i>Behavioural factors</i>
Temporal pattern	General coping style
Accompanying symptoms	Learned pain behaviours
<i>Medical/surgical</i>	Overt distress level
Investigations conducted	Parent's behaviours
Radiological and laboratory results	Physical activities and limitations
Consult results	Social activities and limitations
Analgesic and adjuvant medications (type, dose, frequency, route, length of medication trial)	<i>Emotional factors</i>
<i>Clinical factors</i>	Frustration
Environmental features	Anxiety
Roles of medical and associated health professionals	Fear
Nature of interventions	Denial
Complementary and alternative therapy	Sadness
Documentation of pain	Anger
Criteria for determining analgesic effectiveness	Depression

characteristics should be evaluated as part of the initial clinical examination, with pain intensity and any other characteristics that are clinically relevant for children monitored regularly. Children's descriptions about the nature of their pain (when self-report is available) complete the information obtained through radiological and laboratory investigations. Since several situational factors usually contribute to children's pain, distress, and disability, health care providers should evaluate the extent to which these may be relevant for a child—building on their knowledge of the child and family's previous experiences throughout the child's illness and their observations of the current situation.

In palliative care, the differential diagnosis of a child's pain is a dynamic process that guides our clinical management. We should select specific therapies to target the responsible central and peripheral mechanisms and to mitigate the pain-exacerbating impact of situational factors, recognizing that the multiple causes and contributing factors will vary over time. Drug therapies—analgesics, analgesic-adjuvants, and anaesthetics, are essential for pain control, but non-drug therapies—cognitive, physical, and behavioural, are also essential. As we monitor the child's improvement in response to the therapies initiated, we refine our pain diagnosis and treatment plan accordingly. Pain control is achieved practically by adjusting both drug and non-drug therapies in a rational child-centred manner based on the assessment process, as outlined by the treatment algorithm in Fig. 2. (The different therapies are described later in the chapter.) Controlling children's pain requires an integrated approach because many factors are responsible, no matter how seemingly clear cut the aetiology. Adequate analgesic prescriptions, administered at regular dosing intervals, must be complemented by a practical cognitive-behavioural approach to ensure optimal pain relief.

Misconceptions regarding pain control in children

Several misconceptions have led to inadequate pain control in children as described in the following (revised from ref. 1).

Misconceptions about children's pain systems

Many health care providers continue to treat children's pain from an erroneous disease model perspective wherein pain is always proportional to the extent and severity of tissue damage. As a result of misconceptions about the plasticity and complexity of children's nociceptive systems, they focus on the primary source of noxious stimulation but not on all the causative and contributing factors that affect nociceptive processing. As a result of misconceptions about nociceptive and neuropathic components of pain, they fail to use the wide range of analgesic and analgesic-adjuvants available to control pain.

Misconceptions about the pharmacodynamics and pharmacokinetics of opioid analgesics

As a result of misconceptions about the pharmacodynamics and pharmacokinetics of opioid analgesics, health professionals do not always select the most appropriate drugs, doses, dosing intervals, or administration routes.

Misconceptions about the risk of addiction

Some health care providers and parents believe that opioid analgesics should be administered only as a last resort, to avoid drug addiction. They have not understood that Tolerance + Physical Dependence \neq Addiction. As a result, children have not always received the potent analgesics required to relieve severe pain. Moreover, they may not understand that opioid related side effects should be treated aggressively so that the potential efficacy of these drugs for controlling pain is not compromised by adverse side-effects.

Misconceptions about the efficacy of non-drug therapies

Many health professionals do not realize that relatively simple non-drug strategies can lessen children's pain. As a result, they have not taught children or their parents how to use practical cognitive, physical, and behavioural strategies that are effective for reducing pain, distress, and pain-related

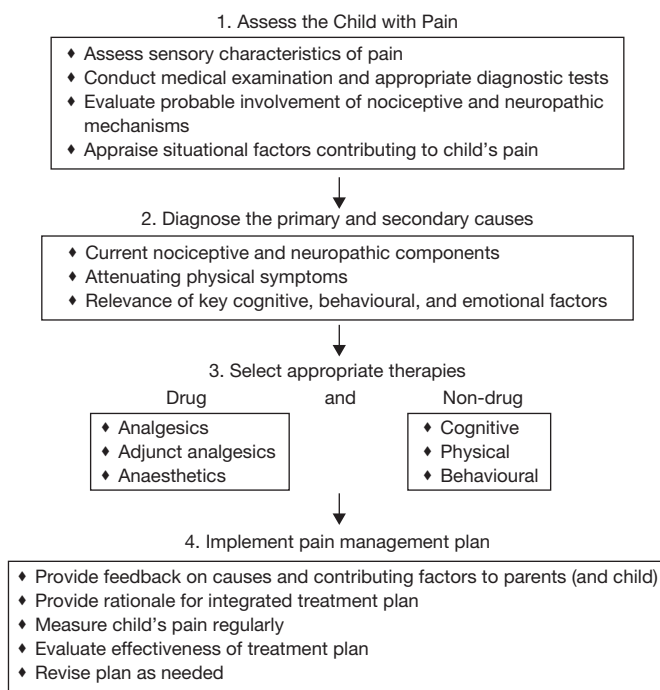


Fig. 2 A treatment algorithm for controlling children's pain.

disability. Similarly, they have not taught parents the importance of evaluating and modifying situational and familial factors to lessen children's pain.

Misconceptions about comprehensive pain control

Many health care providers believe that drug therapies are both necessary and sufficient to control children's pain. They have not prescribed non-drug therapies to supplement or complement analgesics, even when situational factors are impeding analgesic efficacy.

Misconceptions about pain assessment

Many health care providers do not know how to routinely assess children's pain levels or the factors that intensify their pain and distress. As a result, it may be difficult to evaluate the effectiveness of changes in drug therapy, complementary therapies, and situational factors.

Misconceptions about who is in charge of pain control

One individual should assume primary responsibility for ensuring that a child's pain is controlled adequately. Diffusion of responsibility among various health care providers leads to gaps in recognizing a child's pain and treating pain appropriately.

Misconceptions about the importance of consistent pain control

The medical specialties, which provide care to children throughout their illness, do not always adopt a consistent approach to pain assessment and pain control, similar to their consistent approach to disease diagnosis and medical treatment. The failure to regard pain control as important throughout a child's treatment can lead to difficulties for children in palliative care, whose previous experiences with inadequate pain management creates undue stress and anxiety for them and their parents.

Guidelines for assessment, analgesic selection and administration, and non-pharmacological interventions

The principles of analgesic therapy, the guidelines for drug administration, and the guidelines for a supportive cognitive-behavioural approach are those that should be followed in all paediatric palliative care, including the care of children with cancer, neurodegenerative diseases, and acquired human immunodeficiency virus (HIV) infection.

Evaluating children's pain

Pain assessment is an integral component of diagnosis and treatment for children. A thorough medical history, physical examination, and assessment of pain characteristics and contributing factors are necessary to establish a correct clinical diagnosis. Subsequent assessments of pain intensity enable us to determine when treatments are effective and to identify those children for whom they are most effective. Health care providers need pain measures that are convenient to administer and whose resulting pain scores provide meaningful information about children's pain experiences. An extensive array of pain measures have been developed and validated for use with infants, children, and adolescents.^(20–22)

Like adult pain measures, children's pain measures are classified as physiological, behavioural, and psychological, depending on what is monitored—physical parameters (e.g. heart rate, sweat index, blood pressure, cortisol level), distress behaviours (e.g. grimaces, cries, protective guarding gestures), or children's own descriptions of what they are experiencing (e.g. words, drawings, numerical ratings). Physiological and behavioural measures provide indirect estimates of pain because health care providers must infer the location and strength of a child's pain solely from his or her responses. In contrast, psychological measures can provide direct information about the location, strength, quality, affect, and duration.

The criteria for an accurate pain measure are similar to those required for any measuring instrument. A pain measure must be valid, in that it

measures a specific aspect of pain so that changes in pain ratings reflect meaningful differences in a child's pain experience. The measure must be reliable, in that it provides consistent and trustworthy pain ratings regardless of the time of testing, the clinical setting, or who is administering the measure. The measure must be relatively free from bias, in that children should be able to use it similarly, regardless of differences in how they may wish to please adults. The pain measure should be practical and versatile for assessing different types of pain (e.g. disease-related, procedural pain) in many different children (according to age, cognitive level, cultural background) and for use in diverse clinical and home settings.

Physiological and behavioural pain scales

Although physiological parameters can provide valuable information about a child's distress state, more research is required to develop a sensitive system for interpreting how these parameters reflect pain strength. At present, there are no valid physiological pain scales for children.

Most behavioural pain scales are checklists of the different distress behaviours that children exhibit when they experience a certain type of pain.^(20,23,24) To develop these scales, trained health care providers carefully observe children when they are in pain (e.g. after surgery) and document any behaviours that seem caused by the pain. They then list these 'presumed pain' behaviours (e.g. crying, facial expression, limb rigidity) on an itemized checklist. Parents complete the pain scale by checking which of the listed behaviours they see when children are ill. On many scales, parents also rate the intensity of the behaviours. The intensity scores for each of the observed behaviours are summed to produce a composite pain score. Although most behavioural scales measure acute pain, recent attention is focused on the need to develop sensitive measures for children who are cognitively or physically impaired.⁽²⁵⁾

The current behavioural scales may not be adequate for children receiving palliative care. The complexity of a child's disease or health condition, concomitant drug therapy, and the other distress sources in the health care environment, may limit children's ability to behave so that the pain score is not meaningful. Their pain behaviours may be very different from those of the children studied to develop the original scales. Moreover, the most salient pain behaviour might be very child-dependent and vary widely among different children or change throughout the course of their illness. At present, health care providers must use their content expertise and consult with parents to carefully consider which behaviour or behaviours are the most relevant indices of pain for a particular child. They can chart the presence and intensity of these behaviours (it is likely that these will be more subtle indices than on current standardized scales) and interpret them as an indirect measure of pain.

Psychological pain scales

Psychological or self-report pain scales directly capture an individual's subjective experience of pain. Interviews, questionnaires, adjective checklists, and numerous pain intensity scales are available for children, each with some evidence of validity and reliability.^(20,26) Clinical interviews are ideally suited for learning about the sensory characteristics of pain, the aversive component, and contributing cognitive, behavioural, and emotional factors. Interviews should also include a simple rating scale to document pain strength. Children choose a level on the scale that best matches the strength of their own pain (i.e. a level on a number or thermometer scale, a number of objects, a mark on a visual analogue scale, a face from a series of faces varying in emotional expression, or a particular word from adjective lists). Pain intensity scales are easy to administer, requiring only a few seconds once children understand how to use them. Many of these scales yield pain scores on a 0–10 scale. Visual and coloured analogue scales are versatile for use with acute, recurrent, and chronic pain and provide a convenient and flexible pain measure for use in hospital and at home.

Health care providers must consider the age and cognitive ability of a child when selecting a pain scale. Most toddlers (approximately 2 years of age) can communicate the presence of pain, using words learned from their parents to describe the sensations they feel when they hurt themselves. They use concrete analogies to describe their perceptions.

Gradually children learn to differentiate and describe three levels of pain intensity—‘a little’, ‘some or medium’, and ‘a lot’. By the age of 5, most children can differentiate a wider range of pain intensities and many can use simple pain intensity scales.

Children’s understanding and descriptions of pain naturally depend on their age, cognitive level, and previous pain experience. Children begin to understand pain through their own hurting experiences; they learn to describe the different characteristics of their pains (intensity, quality, duration, and location) in the same way that they learn specific words to describe different sounds, tastes, smells, and colours. Most children can communicate meaningful information about their pain. Gradually they develop an increasing ability to describe specific pain features—the quality (aching, burning, pounding, sharp), intensity (mild to severe), duration and frequency (a few seconds to years), location (from a diffuse location on their skin to more precise internal localization), and unpleasantness (mild annoyance to an intolerable discomfort). Children’s understanding of pain and the language that they use to describe pain comes from the words and expressions used by their families and peers and from characters depicted in books, videos, and movies. (For a more extensive review of developmental factors in children’s pain, see refs 1, 6, 27–31.)

Physicians should always ask children directly about their pain. Pain onset, location, frequency (if recurring), quality, intensity, accompanying physical symptoms, and pain related disability should be assessed as part of children’s clinical examination. Health care providers should also assess relevant situational factors in order to modify their pain-exacerbating impact, especially the factors listed in Table 1.

Analgesic selection and administration

Pain control should include regular pain assessments, appropriate analgesics, and adjuvant analgesics administered at regular dosing intervals, adjunctive drug therapy for symptom and side-effects control, and non-drug therapies to modify the situational factors that can exacerbate pain and suffering. Analgesics include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids. Adjuvant analgesics include a variety of drugs with analgesic properties that were initially developed to treat other health problems, such as anticonvulsants and antidepressants. The use of adjuvant analgesics has become a cornerstone of pain control in paediatric palliative care. They are especially crucial when pain has a neuropathic component.

The guiding principles of analgesic administration are ‘by the ladder’, ‘by the clock’, ‘by the child’, and ‘by the mouth’. ‘By the ladder’ refers to a three-step approach for selecting drugs according to their analgesic potency based on the child’s pain level—acetaminophen to control mild pain, codeine to control moderate pain, and morphine for strong pain.⁽³²⁾ The ladder approach was based on our scientific understanding of how analgesics affect pain of nociceptive origins. If pain persists despite starting with the appropriate drug, recommended doses, and dosing schedule, move up the ladder and administer the next more potent analgesic. Even when children require opioid analgesics, they should continue to receive acetaminophen (and NSAIDs, if appropriate) as supplemental analgesics. The analgesic ladder approach is based on the premise that acetaminophen, codeine, and morphine should be available in all countries and that doctors and health care providers can relieve pain in the majority of children with a few drugs.

However, increasing attention is focusing on ‘thinking beyond the ladder’ in accordance with our improved understanding of pain of neuropathic origins.^(33,34) Children should receive adjuvant analgesics to more specifically target neuropathic mechanisms. Regrettably, two of the main classes of adjuvant analgesics, antidepressants and anticonvulsants, have unfortunate names. Proper education of health care providers, parents, and children should lead to a wider acceptance and use of these medications for pain management. For example, amitriptyline may require 4–6 weeks to affect depression, but often requires only 1–2 weeks to affect pain. The newer classes of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), may be beneficial to treat depression for a child with pain but have not been shown to be beneficial for pain management. The other main class

of adjuvant analgesics are the anticonvulsants. The two principal medications used for this purpose in paediatrics are carbamazepine and gabapentin. With gabapentin, the main dose-limiting side-effect is sedation so that a slow titration to maximal dose is required. Because of its greater number of significant side effects, the use of carbamazepine has decreased recently and the use of gabapentin has increased. We still await published studies to support the wide use of gabapentin.

NSAIDs are similar in potency to aspirin. NSAIDs are used primarily to treat inflammatory disorders and to lessen mild to moderate acute pain. They should be used with caution in patients with hepatic or renal impairment, compromised cardiac function, hypertension (since they may cause fluid retention, oedema), and a history of GI bleeding or ulcers. NSAIDs may also inhibit platelet aggregation and thus must be monitored closely in patients with prolonged bleeding times. Indications for NSAIDs are much narrower for children with cancer (due to the concern for bleeding problems) than for children with other painful conditions. Although acetaminophen should be considered the routine non-opioid analgesic for children with cancer, NSAIDs are effective for patients with bony metastases, who have adequate platelets.

Although the specific drugs and doses are determined by the needs of each child, general guidelines for drug therapies to control pain for children in palliative care have been developed through a Consensus Conference on the Management of Pain in Childhood Cancer, published as a supplement to *Pediatrics*,⁽³⁵⁾ in a monograph, *Cancer Pain Relief and Palliative Care for Children*,⁽¹⁴⁾ and in clinical practice guidelines.^(36–38) The drugs listed in this chapter are based on these sources and guidelines from our institution.⁽³⁹⁾ Recommended starting doses for analgesic medications to control children’s disease-related pain are listed in Tables 3 and 4; starting doses for adjuvant analgesic medications to control pain, drug related side-effects, and other symptoms are listed in Table 5. (For further review of analgesics and adjuvant analgesics in children, see refs 34, 40–44.)

Children should receive analgesics at regular times, ‘by the clock’, to provide consistent pain relief and prevent breakthrough pain. The specific drug schedule (e.g. every 4 or 6 h) is based on the drug’s duration of action and the child’s pain severity. Although breakthrough pain episodes have been recognized as a problem in adult pain control, they may represent an even more serious problem for children. Unlike adults, who generally realize that they can demand more potent analgesic medications or demand more frequent dosing intervals, children have little control, little awareness of alternatives, and fear that their pain cannot be controlled. They may become progressively frightened, upset, and preoccupied with their symptoms. Thus, it is essential to establish and maintain a therapeutic window of pain relief for children.

Analgesic doses should be adjusted ‘by the child’. There is no one dose that will be appropriate for all children with pain. The goal is to select a dose that prevents children from experiencing pain before they receive the next dose. It is essential to monitor the child’s pain regularly and adjust analgesic doses as necessary to control the pain. The effective opioid dose to relieve pain varies widely among different children or in the same child at different times. Some children require massive opioid doses at frequent intervals to control their pain. If such large doses are necessary for effective pain control, and the side-effects can be managed by adjunctive medication so that children are comfortable, then the doses are appropriate. Children receiving opioids may develop altered sleep patterns so that they are awake at night, fearful and complaining about pain, and they sleep intermittently throughout the day. They should receive adequate analgesics at night with antidepressants or hypnotics as necessary to enable them to sleep throughout the night. To relieve severe ongoing pain, opioid doses should be increased steadily until comfort is achieved, unless the child experiences unacceptable side-effects such as somnolence or respiratory depression (Table 6).

‘By the mouth’ refers to the oral route of drug administration. Medication should be administered to children by the simplest and most effective route, usually by mouth. Since children are afraid of painful injections they may deny that they have pain or they may not request

Table 3 Non-opioid drugs for relieving cancer pain in children

Drug	Dosage	Comments
Acetaminophen	10–15 mg/kg PO, every 4–6 h	Lacks gastrointestinal and haematological side-effects; lacks anti-inflammatory effects (may mask infection-associated fever) Dose limit of 65 mg/kg/day or 4 g/day, whichever is less
Ibuprofen	5–10 mg/kg PO, every 6–8 h	Anti-inflammatory activity Use with caution in patients with hepatic or renal impairment, compromised cardiac function or hypertension (may cause flu retention, oedema), history of GI bleeding or ulcers, may inhibit platelet aggregation Dose limit of 40 mg/kg/day; max. dose of 2400 mg/day
Naproxen	10–20 mg/kg/day PO, divided every 12 h	Anti-inflammatory activity. Use with caution and monitor closely in patients with impaired renal function. Avoid in patients with severe renal impairment Dose limit of 1 g/day
Diclofenac	1 mg/kg PO, every 8–12 h	Anti-inflammatory activity. Similar GI, renal, and hepatic precautions as noted above for ibuprofen and naproxen Dose limit of 50 mg/dose

Note: Increasing the dose of non-opioids beyond the recommended therapeutic level produces a 'ceiling effect', in that there is no additional analgesia but there are major increases in toxicity and side-effects.

PO, by mouth; GI, gastrointestinal.

Table 4 Opioid analgesics: usual starting doses

Drug	Equianalgesic dose (parenteral)	Starting dose IV	IV : PO ratio	Starting dose PO/transdermal	Duration of action
Morphine	10 mg	Bolus dose = 0.05–0.1 mg/kg every 2–4 h Continuous infusion = 0.01–0.04 mg/kg/h	1 : 3	0.15–0.3 mg/kg/dose every 4 h	3–4 h
Hydromorphone	1.5 mg	0.015–0.02 mg/kg every 4 h	1 : 5	0.06 mg/kg every 3–4 h	2–4 h
Codeine	120 mg	Not recommended		1.0 mg/kg every 4 h (dose limit 1.5 mg/kg/dose)	3–4 h
Oxycodone	5–10 mg	Not recommended		0.1–0.2 mg/kg every 3–4 h	3–4 h
Meperidine ^a	75 mg	0.5–1.0 mg/kg every 3–4 h	1 : 4	1.0–2.0 mg/kg every 3–4 h (dose limit 150 mg)	1–3 h
Fentanyl ^b	100 µg	1–2 µg/kg/h as continuous infusion		25 µg patch	72 h (patch)
Controlled-release morphine ^{c,d}				0.6 mg/kg every 8 h or 0.9 mg/kg every 12 h	
Controlled-release hydromorphone ^d				0.18 mg/kg every 12 h	
Controlled-release codeine ^d				3 mg/kg every 12 h	
Controlled-release oxycodone ^d				0.3–0.6 mg/kg every 12 h	
Methadone	10 mg	0.1 mg/kg every 4–8 h	1.2	0.2 mg/kg every 4–8 h	12–50 h

Doses are for opioid naïve patients. For infants under 6 months, start at one-quarter to one-third the suggested dose and titrate to effect.

PO, by mouth; IV, intravenous.

Principles of opioid administration:

1. If inadequate pain relief and no toxicity at peak onset of opioid action, increase dose in 50% increments.
2. Avoid IM administration.
3. Whenever using continuous infusion, plan for hourly rescue doses with short onset opioids if needed. Rescue dose is usually 50–200% of continuous hourly dose. If greater than six rescues are necessary in 24-h period, increase daily infusion total by the total amount of rescues for previous 24 h ÷ 24. An alternative is to increase infusion by 50%.
4. To change opioids—because of incomplete cross-tolerance: if changing between opioids with short duration of action, start new opioid at 50% of equianalgesic dose. Titrate to effect. If changing between opioids from short to long duration of action (i.e. morphine to methadone), start at 25% of equianalgesic dose and titrate to effect.
5. To taper opioids—anyone on opioids over 1 week must be tapered to avoid withdrawal: taper by 50% for 2 days, and then decrease by 25% every 2 days. When dose is equianalgesic to an oral morphine dose of 0.6 mg/kg/day may be stopped. Some patients on opioids for prolonged periods, may require much slower weaning.

^a Avoid use in renal impairment. Metabolite may cause seizures.

^b Potentially highly toxic. Not for use in acute pain control.

^c Use may be hampered by child's difficulty in swallowing large tablets.

^d The widely equianalgesic doses in adults are used as guidelines in paediatric practice but have not been substantiated in children.

Table 5 Adjuvant analgesic drugs

Drug category	Drug, dosage	Indications	Comments
Antidepressants	Amitriptyline, 0.2–0.5 mg/kg PO. Titrate upward by 0.25 mg/kg every 2–3 days. Maintenance: 0.2–3.0 mg/kg Alternatives: nortriptyline, doxepin, imipramine, venlafaxine	Neuropathic pain (i.e. vincristine-induced, radiation plexopathy, tumour invasion, CRPS-1) Insomnia	Usually improved sleep and pain relief within 3–5 days Anticholinergic side-effects are dose-limiting. Use with caution for children with increased risk for cardiac dysfunction
Anticonvulsants	Gabapentin, 5 mg/kg/day PO. Titrate upward over 3–7 days. Maintenance: 15–50 mg/kg/day PO divided TID Carbamazepine, initial dosing: 10 mg/kg/day PO divided OD or BID. Maintenance: up to 20–30 mg/kg/day PO divided every 8 h. Increase dose gradually over 2–4 weeks Alternatives: phenytoin, clonazepam	Neuropathic pain, especially shooting, stabbing pain	Monitor for haematological, hepatic, and allergic reactions Side-effects: gastrointestinal upset, ataxia, dizziness, disorientation, somnolence
Sedatives, hypnotics, anxiolytics	Diazepam, 0.025–0.2 mg/kg PO every 6 h Lorazepam, 0.05 mg/kg/dose SL Midazolam, 0.5 mg/kg/dose PO administered 15–30 min prior to procedure; 0.05 mg/kg/dose IV for sedation	Acute anxiety, muscle spasm Premedication for painful procedures	Sedative effect may limit opioid use. Other side-effects include: depression and dependence with prolonged use
Antihistamines	Hydroxyzine, 0.5 mg/kg PO every 6 h Diphenhydramine, 0.5–1.0 mg/kg PO/IV every 6 h	Opioid-induced pruritus, anxiety, nausea	Sedative side-effects may be helpful
Psychostimulants	Dextroamphetamine, Methylphenidate, 0.1–0.2 mg/kg BID Escalate to 0.3–0.5 mg/kg as needed	Opioid-induced somnolence Potentiation of opioid analgesia	Side-effects include agitation, sleep disturbance, and anorexia Administer second dose in afternoon to avoid sleep disturbances
Corticosteroids	Prednisone, prednisolone, and dexamethasone dosage depends on clinical situation (i.e. dexamethasone initial dosing: 0.2 mg/kg IV. Dose limit 10 mg. Subsequent dose 0.3 mg/kg/day IV divided every 6 h)	Headache from increased intracranial pressure, spinal, or nerve compression; widespread metastases	Side-effects include oedema, dyspeptic symptoms, and occasional gastrointestinal bleeding

CRPS-1, complex regional pain syndrome, Type 1; PO, by mouth; IV, intravenous; SL, sublingual.

medication. When possible, children should receive medications through routes that do not cause additional pain. Although optimal analgesic administration for children requires flexibility in selecting routes according to children's needs, parenteral administration is often the most efficient route for providing direct and rapid pain relief. Since intravenous, intramuscular, and subcutaneous routes cause additional pain for children, serious efforts have been expended on developing more pain-free modes of administration that still provide relatively direct and rapid analgesia. Attention has focused on improving the effectiveness of oral routes. As an example, oral transmucosal fentanyl citrate (OTFC) provides rapid onset analgesia via a pleasant route for children with cancer receiving painful medical procedures. OTFC produces significant serum concentrations after 15–20 min.⁽⁴⁵⁾ Children aged 2–14 years have shown good cooperation and sedation when given OTFC as a premedication.^(46,47) OTFC produced safe and effective analgesia for outpatient wound care in children and the taste was preferred to oral oxycodone.⁽⁴⁸⁾

Many hospitals have restricted the use of intramuscular injections because they are painful and drug absorption is not reliable; they advocate the use of intravenous lines into which drugs can be administered directly without causing further pain. Topical anaesthetic creams should also be applied prior to the insertion of intravenous lines in children. The use of portacatheters has become the gold standard in paediatrics, particularly for children with cancer who require administration of multiple drugs at weekly intervals.

Continuous infusion has several advantages over intermittent subcutaneous, intramuscular, or intravenous routes. This method circumvents

repetitive injections, prevents delays in analgesic drug administration, and provides continuous levels of pain control without children experiencing increased side-effects at peak level and pain breakthroughs at trough level. Continuous infusion should be considered when children have pain for which oral and intermittent parenteral opioids do not provide satisfactory pain control, when intractable vomiting prevents oral medications, when intravenous lines are not desirable, and when children would like to remain at home despite severe pain. Children receiving a continuous infusion should continue to receive 'rescue doses' to control breakthrough pain, as necessary. As outlined in Table 4, the rescue doses should be 50–200 per cent of the continuous infusion hourly dose. If children experience repeated breakthrough pain, the basal rate can be increased by 50 per cent or by the total amount of morphine administered through the rescue doses over a 24-h period (divided by 24 h).

Patient-controlled analgesia (PCA) enables children to administer analgesic doses according to their pain level. PCA provides children with a continuum of analgesia that is prompt, economical, not nurse dependent and a lower overall narcotic use.^(49–54) It has a high degree of safety, allows for wide variability between patients and there is no delay in analgesic administration (for review, see ref. 49). It can now be regarded as a standard for the delivery of analgesia in children aged more than 5 years.⁽⁵⁵⁾ However, there are opposing views about the use of background infusions with PCA. Although they may improve efficacy, they may increase the occurrence of adverse effects such as nausea and respiratory depression. In a comparison of PCA with and without a background infusion for children having lower extremity surgery, the total morphine requirements were reduced in the

Table 6 Opioid side-effects

Side-effect	Management
Respiratory depression	Reduction in opioid dose by 50%, titrate to maintain pain relief without respiratory depression
Respiratory arrest	Naloxone, titrate to effect with 0.01 mg/kg/dose IV/ETT increments or 0.1 mg/kg/dose IV/ETT, repeat PRN. Small frequent doses of diluted naloxone or naloxone drip preferable for patients on chronic opioid therapy to avoid severe, painful withdrawal syndrome. Repeated doses often required until opioid side-effect subsides
Drowsiness/sedation	Frequently subsides after a few days without dosage reduction; methylphenidate or dextroamphetamine (0.1 mg/kg administered twice daily, in the morning and mid-day so as not to interfere with night-time sleep). The dose can be escalated in increments of 0.05–0.1 mg/kg to a maximum of 10 mg/dose for dextroamphetamine and 20 mg/dose for methylphenidate
Constipation	Increased fluids and bulk, prophylactic laxatives as indicated
Nausea/vomiting	Administer an antiemetic (e.g. ondansetron, 0.1 mg/kg IV/PO every 8 h) Antihistamines (e.g. dimenhydrinate 0.5 mg/kg/dose every 4–6 h IV/PO) may be used. Pre-chemotherapy, Nabilone 0.5–1.0 mg PO and then every 12 h may also be used
Confusion, nightmares, hallucinations	Reassurance only, if symptoms mild. A reduced dosage of opioid or a change to a different opioid or add neuroleptic (e.g. haloperidol 0.1 mg/kg PO/IV every 8 h to a maximum of 30 mg/day)
Multifocal myoclonus; seizures	Generally occur only during extremely high dose therapy; reduction in opioid dose indicated if possible. Add a benzodiazepine (e.g. clonazepam 0.05 mg/kg/day divided BID or TID increasing by 0.05 mg/kg/day every 3 days PRN up to 0.2 mg/kg/day. Dose limit of 20 mg/day)
Urinary retention	Rule out bladder outlet obstruction, neurogenic bladder, and other precipitating drug (e.g. tricyclic antidepressant). Particularly common with epidural opioids. Change of opioid, route of administration, and dose may relieve symptom. Bethanechol or catheter may be required

IV, intravenous; PO, by mouth; ETT, endotracheal tube; PRN, as needed.

PCA only group and the background infusion offered no advantage.⁽⁵⁶⁾ In another study comparing background infusion and PCA, children between 9 and 15 achieved better pain relief with PCA while children between 5 and 8 showed no difference.⁽⁵⁷⁾ Although data on the use of background infusions in combination with PCA for the paediatric palliative care patient is limited, our current standard is to add a background infusion to the PCA if the pain is not controlled adequately with PCA alone. The selection of opioid used in PCA is perhaps less critical than the appropriate selection of parameters such as bolus dose, lockout, and background infusion rate. The opioid choice may be based on adverse effect profile rather than efficacy. Clearly, patient controlled analgesia offers special advantages to children who have little control and who are extremely frightened about uncontrolled pain. PCA is as it states, patient controlled analgesia. When special circumstances require that alternate people administer the medication, we do allow both nurse and parent controlled analgesia. Under these circumstances, parents require our nurse educators to fully educate them on the use of PCA.

Fentanyl is a potent synthetic opioid, which like morphine binds to mu receptors. However, fentanyl is 75–100 times more potent than morphine. The intravenous preparation of fentanyl has been used extensively in children. A transdermal preparation of fentanyl was introduced in 1991 for use with chronic pain. This route provides a noninvasive but continuously controlled delivery system. Although limited data is available on transdermal fentanyl (TF) in children, its use is increasing for children with stable and chronic cancer pain. In a recent study, TF was well tolerated with effective pain relief in 11 of 13 children and provided an ideal approach for children where compliance with oral analgesics was problematic.⁽⁵⁸⁾ Children in palliative care were converted from oral morphine doses to TF; the investigators noted diminished side-effects and improved convenience with TF.⁽⁵⁹⁾ The majority of parents and investigators considered TF to be better than previous treatment. No serious adverse events were attributed to fentanyl, suggesting that TF was both effective and acceptable for children and their families. Similarly, no adverse effects were noted in a study of TF for children with pain due to sickle cell crisis.⁽⁶⁰⁾ This study showed a significant relationship between TF dose and fentanyl concentration; pain control with the use of TF was improved in seven of 10 patients in comparison to PCA alone. In a multicentre crossover study in adults, TF caused significantly less constipation and less daytime drowsiness in comparison to

morphine, but greater sleep disturbance and shorter sleep duration.⁽⁶¹⁾ Of those patients able to express a preference, significantly more preferred fentanyl patches. As with all opioids, fatal adult complications have been noted with the use of multiple transdermal patches.⁽⁶²⁾

The use of regional techniques (epidural and spinal) for the administration of local anaesthetics and analgesics for children continues to be an integral part of pain control in children.⁽⁶³⁾ Experience from many centres suggests that these techniques can be extremely useful for children with advanced cancer with resulting pain that may be difficult to control by more conventional means. It is also feasible for children to receive epidural and spinal infusions at home on an extended basis.

When one undertakes the administration of potent analgesics and anaesthetics, whether by intravenous or a regional anaesthetic technique such as an epidural or spinal approach, appropriate monitoring must be paramount for the safety of our patients. This involves the education and training of staff; immediate availability of resuscitative drugs and equipment; and an accurate and timely pain record consisting of vitals signs, pain and sedation scores. A complete set of intravenous and epidural monitoring guidelines have been included in Table 7.

Dosing considerations for neonates and infants

Recent research on controlling pain in neonates has led to improved rational therapeutic regimens to provide safe and effective analgesia with a minimum of side-effects.^(64–71) Neonates and infants require the same three categories of analgesic drugs as older children. However, the differences in pharmacokinetics and pharmacodynamics among neonates, pre-term infants, and full-term infants, warrant special dosing considerations for infants and close monitoring when they receive opioids. Acetaminophen can be safely administered to neonates and infants without concern for hepatotoxicity, when given for short courses at the recommended dose (10–15 mg/kg PO). The rate of absorption is slower in neonates and its plasma half-life prolonged, so peak serum concentrations are reached at approximately 60 min after an oral dose, and subsequent doses may be required after 6 h rather than 4 h. Acetaminophen does not cause respiratory depression and does not produce tolerance.

Opioid analgesics are the mainstay of treatment for controlling severe pain in neonates. When compared to Table 4, the starting doses for opioid

Table 7 Analgesia monitoring guidelines

<i>Baseline assessment</i>
Obtain RR, HR, BP, O ₂ saturation, sedation score, and pain score before administering a single or intermittent dose or initiating continuous infusion
<i>Intermittent intravenous administration</i>
RR, HR, BP, and sedation score every 5 min × 4, then every 30 min × 2, and then as per child's condition/pre-existing orders
Pain score every 20–30 min
Continuously monitor O ₂ saturation only for children whose underlying condition predisposes them to respiratory depression
<i>Intravenous additive (to run over 15–20 min)</i>
RR, HR, BP, and sedation score every 10 min × 2, then every 30 min × 2, and then as per child's condition
Pain score at completion of the flush, then every 30 min × 2, and then as per child's condition/pre-existing orders
Continuously monitor O ₂ saturation only for children whose underlying condition predisposes them to respiratory depression
<i>Continuous IV infusion/PCA</i>
RR, HR, BP, pain score, and sedation score every 1 h × 4, then RR and sedation score every 1 h, and then HR, BP, and pain score every 4 h
Continuously monitor O ₂ saturation and document reading every 1 h
<i>Intermittent epidural administration</i>
RR, HR, and BP every 5 min for the first 20 min following a bolus dose, and then RR and sedation score every 1 h
HR, BP, pain score, and motor block score every 4 h
Continuously monitor only for children whose underlying condition predisposes them to respiratory depression
<i>Continuous epidural infusion^{a,b}</i>
RR, HR, BP, sedation score, pain score, and motor block score every 1 h × 4 h, then RR and sedation score every 1 h, and HR, BP, pain score, and motor block score every 4 h
Continuously monitor O ₂ saturation and document reading every 1 h

^a Opioids used with bupivacaine.

^b Note: After any change in drug dose, infusion rate or if transferred between patient care areas, return to assessments every 1 h for 4 h.

Continuous respiratory rate/apnoea monitoring may provide additional benefits for certain children who are receiving continuous opioid infusions by alerting the nurse to a decreasing respiratory rate. Respiratory rate monitoring is not, however, a substitute for frequent patient observation and vital sign monitoring

ECG monitoring is not routinely required, but may be ordered if the child's underlying condition predisposes them to ECG abnormalities.

Source: Adapted from 2001–2002 Drug Formulary, The Hospital for Sick Children, Toronto, Ontario.

analgesics in infants under 6 months of age are one-quarter to one-third the suggested doses. As for children, the dosage and mode of administration of opioids needs to be titrated between the degree of analgesia required and a reasonable level of sedation. (Note: theoretically postulated long-term effects of opioid administration include the alteration of endogenous opioid receptor development but these effects are irrelevant in neonatal palliative care.) The drug clearance and the analgesic effects of morphine, fentanyl, sufentanil, and methadone for infants above the age of 6 months and children resemble those for young adults. Thus, the general clinical impression is that morphine and other opioids have a reasonable margin of safety and excellent efficacy for most children over 6 months of age with cancer pain. However, premature and term newborns show reduced clearance of most opioids. The widely observed sensitivity of new-borns to morphine is probably due to kinetic factors, including smaller volume of distribution, diminished clearance, immaturity of the blood–brain barrier, and increased sensitivity on a pharmacodynamic basis associated with the immaturity of ventilatory responses to hypoxaemia and hypercarbia. Therefore, opioids must be used more cautiously with infants under the age of 6 months and appropriate monitoring must be instituted. Proper dosing and careful monitoring will help minimize side-effects. Tolerance has significance only as a signal of receptor function or a potential indicator of withdrawal when therapy is discontinued.

Neonates who have pain severe enough to require opioids usually have an intravenous line in place. If a limited number of doses is needed and if intravenous access is not available, intramuscular or subcutaneous routes may be used occasionally in full term neonates. However, these routes are painful and not suitable for preterm neonates because of their sparse muscle mass and delicate skin. They are also not suitable for long-term pain management in term neonates because plasma levels and clinical effects are less controlled and difficult to titrate from intramuscular administrations. Similarly, intravenous doses may produce peak levels resulting in coma and respiratory depression with rapid decline in plasma levels, causing alternate periods of pain and analgesia. Thus, continuous intravenous infusion of

opioids, producing constant blood levels and minimal fluctuations in analgesia, is the most effective route. The use of peripherally inserted central catheters (PICCs) has become standard practice for the neonate with difficult venous access or for the patient that may require access for a prolonged period. Anand et al. recommend a loading dose of 50 µg/kg followed by a continuous infusion of morphine at 10–20 µg/kg/h.⁽⁶⁴⁾ Further increases in the infusion rate may be required to titrate to clinical effect or with the development of tolerance. However, infants must be monitored carefully because most opioids have prolonged duration of action in neonates, so that continuous infusions can result in slow accumulation of the drug over time with high blood levels that may not be detected immediately.

The principal and potentially life threatening side-effect of all opioid drugs is the dose-dependent respiratory depression leading to apnoea, which may be observed in infants and neonates at relatively low doses. This is advantageous in ventilated patients, but poses considerable challenges when using opioids for spontaneously breathing newborns. Opioid-induced respiratory depression can be reversed with naloxone, but the effect of the drug diminishes within 30 min so that repeated naloxone dosing may be required. If apnoea does occur, stimulation of the baby will usually elicit some respiratory effort temporarily while emergency arrangements are made to inject naloxone and provide respiratory support. Naloxone should be titrated to effect in increments of 10 µg/kg until a desired effect is obtained, or up to a total dose of 100 µg/kg. High doses of naloxone may produce a massive stress response from sudden nociception and withdrawal, or may result in undesirable fluid shifts. Following an effective dose of naloxone, the neonate should be monitored closely for at least 24 h. In fact, because plasma concentrations of morphine can increase in some neonates, even after an opioid infusion is discontinued, neonates require close monitoring for at least 24 h after morphine administration is discontinued.

Young infants, especially premature babies or those who have neurological abnormalities or pulmonary disease, are more susceptible to apnoea and respiratory depression when systemic opioids are used. The infants'

metabolism is altered so that the elimination half-life is longer and there may be possible increased entry into the brain, due to immaturity of the blood–brain barrier. Both factors result in young infants having higher concentrations of opioids in the brain for a given dose than mature infants or adults. Thus, non-ventilated infants who are less than 1 year of age should be monitored closely when they receive opioids because extreme sedation and decreased respiratory effort may be difficult to assess. Institutions where neonates and infants are treated for cancer should train personnel in the safe and effective administration of analgesia and provide appropriate technologies for monitoring. Monitoring should include respiratory rate, heart rate, effort, blood pressure, sedation score and pain score, as shown in Table 7.

Epidural analgesia is now widely used for infants with postoperative pain. The haemodynamic effects of major regional analgesia in infants with postoperative pain appear minimal. For paediatric epidural infusions, the standard local anaesthetic we use is bupivacaine in an infusion rate of 0.2–0.4 mg/kg/h. Epidural infusions that exceed the recommended rate may lead to convulsions. Epidural opioids such as morphine and fentanyl have been used successfully, even for very young infants with cancer. The proper use of infusions or intermittent doses of epidural opioids or local anaesthetics requires expertise and appropriate monitoring, as shown in Table 7.

Physical dependence, tolerance, and addiction

Physical dependence is defined as a state of adaptation that often includes tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decrease in the blood level of drug, and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following four Cs: impaired Control over drug use, Compulsive use, continued use despite harm (Consequences), and Craving.⁽⁷²⁾

The fear of opioid addiction in children has been greatly exaggerated. While physical dependence is common, gradual tapering protocols can control the withdrawal syndromes caused by an abrupt cessation of the medication. Physical dependence may develop in as short a period as 7–10 days. Tolerance is also an expected change to be seen and anticipated in children. There is no empirical evidence that children receiving opioid analgesics for pain control are at risk for addiction. In contrast, children who do not receive appropriate analgesic medications are probably more at risk for 'pseudoaddiction' by becoming excessively concerned about receiving their next medication dose in the hope that they might eventually relieve their suffering.

Parents, and occasionally staff, may have misconceptions about the use of potent opioids. Although the sensory characteristics of children's pain should be consistent with the known pattern from the presumed source of tissue injury, the source is not easily identified for all children. This is particularly true for children who have cancer, since there may be multiple sources of noxious stimulation due to disease and the effects of curative therapies. Yet, children's pain must be controlled, even when the specific aetiology is not yet determined. Otherwise, children become increasingly anxious, fearful, and distressed—beginning a cycle of increasing pain that will be more difficult to alleviate.

Parents are often anxious about opioids for their children, particularly when children require increased dose increments. Staff must educate parents that physical dependence and tolerance are very different from addiction. Parents will then understand that physical dependence and tolerance are normal drug effects; they do not mean that their children with pain have become addicted. Physical drug dependence is well recognized. When opioids are suddenly withdrawn, children may suffer from irritability, anxiety, insomnia, diaphoresis, rhinorrhoea, nausea, vomiting, abdominal cramps, and diarrhoea. These withdrawal symptoms can be prevented by

the gradual tapering of an opioid. Even though children with severe pain require progressively higher and more frequent opioid doses due to drug tolerance, they should receive the doses they need to relieve their pain. However, children who require increased opioids to relieve previously controlled pain should be assessed carefully to determine whether the disease has progressed, since pain may be the first sign of advancing disease.

Therapists can use familiar analogies to explain dependence, tolerance, and addiction. For example parents are often accustomed to drinking coffee in the morning. They know that they will experience some noticeable effects without their usual caffeine intake, but they also know that they can withdraw from coffee by gradually lowering their daily consumption. The fact that their body is used to a certain amount of caffeine at certain times of the day means that they are dependent. Similarly, many people become accustomed to a certain level of salt for a food to taste 'salty'. After a while they may need to increase their salt intake if they want foods to taste the same, because their bodies have adjusted to or now tolerate the previous amount of salt so that it no longer has the same effect. In the same way, their children can become tolerant to a morphine dose so that they require a slightly higher dose to achieve the same pain reduction. These benign examples of a body's normal responses to substances often help parents understand that when opioids are prescribed for their children the effects of those drugs are well known, well understood, and will not lead to adverse effects, including addiction.

Opioid-related side-effects

The safe, rational use of opioid analgesics requires an understanding of their clinical pharmacology. The potent opioids that we use to treat children for palliative pain control have no fixed upper dosage limit. The dose can be increased as necessary to maximize pain control, as long as children do not experience dose-limiting side-effects (i.e. vomiting, respiratory depression). The goal should be titrating medication either up or down for maximum clinical effect. Side-effects must be anticipated and treated aggressively. Since opioids produce physical dependence and tolerance, doses must be increased over time to control pain. Doses must be adjusted according to the child's need depending on pain severity, prior analgesic medication use, and the bioavailability and drug distribution of the medication.

All opioids have a similar spectrum of side-effects. These well-known problems should be anticipated and treated whenever opioids are administered, so that children can receive pain control without suffering untoward effects. Children may not report all side-effects (i.e. constipation, dysphoria) voluntarily, so they should be asked specifically about these problems. Some side-effects may resolve within the first 1 or 2 weeks of initiating therapy as the child develops tolerance to them (e.g. nausea, vomiting, and drowsiness). The clinician must educate the patient about these problems and encourage them to give the medication an adequate trial. Slow titration may minimize this problem. Other side-effects may require aggressive treatment. If they persist despite appropriate interventions, conversion to an alternate opioid may be indicated. There is generally incomplete cross-tolerance between opioids, so that the guidelines for converting from one opioid to another is to begin at the lower dosing range, considering the presence or absence of central nervous system side-effects, and titrate upward. When used in therapeutic doses, opioids have not been demonstrated to cause long-term permanent organ toxicity. This makes them a safe choice for use in children. There is evidence that untreated severe chronic pain may cause cognitive impairment, which is improved with opioid therapy. The treatment of opioid side-effects is summarized in Table 6.

Non-drug therapies

Cognitive and behavioural approaches

An extensive array of non-drug therapies are available to treat children's pain, including counselling, guided imagery, hypnosis, biofeedback, behavioural management, acupuncture, massage, homeopathic remedies, naturopathic approaches, and herbal medicines. Non-drug therapies are generally regarded as safe, with few contra-indications for their use in otherwise

healthy children. However, little is known about the safety and effectiveness of certain therapies for children in palliative care. In particular, almost no pediatric research has been conducted on many of the therapies regarded as complementary to traditional medical approaches. Thus, the efficacy of complementary therapies for treating children's pain is unknown, even though children are increasingly using complementary therapies.⁽⁷³⁾ In contrast, the evidence base supporting the efficacy of cognitive and behavioural approaches is strong.^(4,5,14,74–85) These methods can mitigate some of the factors that intensify pain, distress, and disability for children in palliative care.

The primary cognitive and behavioural therapies are listed in Table 8. Cognitive therapies are directed at a child's beliefs, expectations, and coping abilities. They encompass a wide range of approaches from basic patient education to formal psychotherapy. Most children and families benefit from supportive counselling. Accurate information about what will happen and what children may feel should improve children's understanding, increase their control, lessen their distress, and reduce their pain.

In addition, health care providers can teach children how to use a few pain control methods to lessen pain and guide families to recognize the particular circumstances that exacerbate pain and distress. These methods provide children with some independent strategies—either to relieve mild pain or to complement the medication needed to relieve strong pain. Children should begin by learning a few basic methods. As they acquire confidence in using these methods, they seem to naturally adapt them to fit their personality or invent new equally effective methods. A therapist guides them throughout this process. Children should be interested and motivated in learning some independent pain control methods. They seem more adept than adults at using non-drug therapies, presumably because they are usually less biased than adults about their potential efficacy.

Distraction is a simple and effective pain control method. When children intently attend to something other than their pain, they can lessen its intensity and unpleasantness. Distraction is often incorrectly perceived as a simple diversionary tactic; the implication is that the pain is still there but the child is momentarily focused elsewhere. However, when children's attention is fully absorbed in some engaging topic or activity, distraction is a very active process that can reduce the neuronal responses to a noxious stimulus. Children do not simply ignore their pain, but are actually reducing it. The essential feature for achieving pain relief is a child's ability to attend fully to and concentrate on something else besides the pain. Therefore, the choice of a distraction is crucial and varies according to children's ages and interests. Young children usually need to be actively involved with their parents or peers, while older children and adolescents can distract themselves more independently. Children should work with their parents or a therapist to choose distracting activities that children can practically incorporate into their lives. Guided imagery is a specific method of distraction and

attention. A health care provider guides children to concentrate fully on the image of an experience or situation. Children recall and vividly describe what they experienced—the colours, sounds, tastes, and feel of the situation. Children are guided to become as immersed in their image as if it were occurring in the present situation.

There is considerable overlap among the interventions of attention/distraction, guided imagery, and hypnosis. Hypnosis usually begins with an induction procedure in which a child's full attention is focused gradually on the therapist and his/her suggestions. The therapist guides the child into a very relaxed physical and mental state, an altered level of consciousness—distinct from an alert or sleep state. The induction procedure typically includes guided imagery for children and progressive muscle relaxation for adolescents. The induction can be very simple for young children. They can be guided into a hypnotic state as they vividly imagine their favourite television shows, movies, books, or cartoon characters.^(86–88) As they imagine an activity, scene or character, they gradually receive suggestions for relaxation, reduced anxiety, increased control, and pain reduction. The therapist provides consistent positive suggestions, rather than authoritative commands. The emphasis is on the child's own natural abilities, as in 'Notice that your back, legs (painful body areas) feels lighter, the heaviness and pain are starting to lessen. It seems as if your back doesn't hurt as much as before. You are doing well at turning down the pain switch'.

During a hypnotic state, individuals become extremely susceptible to suggestions, including suggestions for pain relief. Children become so involved in thoughts or ideas that they dissociate from a 'reality orientation'.⁽⁸⁷⁾ Hypnosis enables children to re-direct attention from the painful sensation or to reinterpret the sensation as something more pleasant/less aversive and/or less bothersome.⁽⁸⁸⁾ Like adults, children differ in their ability to be hypnotized. Children's ability to use their imagination is the key component in determining their hypnotic susceptibility.

Behaviour therapy is often used in combination with cognitive therapy. The goals are to lessen the specific behaviours (i.e. child, family, and staff) that may increase pain, distress, or disability, while concomitantly increasing healthy behaviours that engage children in living as fully as possible. Relaxation training is a common method used for children with chronic pain. Therapists train children how to achieve a state of mental and physical relaxation so that children can eventually relax independently when they experience pain or feel stressed and fearful about their condition. Therapists may use guided imagery, hypnosis, deep breathing, or progressive relaxation exercises to train children. Biofeedback is a useful tool for teaching children to recognize when their bodies are relaxed. Surface electrodes, attached to the skin or specific muscle groups, transform the electrical activity of the body into easily observable signals.

Pain control methods

Health professionals and parents can relieve children's pain, not only by administering analgesic drugs, but also by increasing their understanding and control, decreasing their emotional distress, and teaching them some simple methods to reduce their pain and anxiety. In addition to providing support and reassurance, parents can help children to understand what will happen, make choices, gain whatever control is possible within the setting, and independently use pain reducing methods. Thus, the family, as well as health professionals, share a fundamental role in managing their children's cancer pain. The key concept underlying the use of all analgesic and non-analgesic therapies for children is 'by the child', as described above.

Specific pain control methods that require the child to concentrate and focus attention should always be used for children with cancer pain. Beales noted critical differences between adults and children in their perceptions of pain, especially cancer pain.⁽⁸⁹⁾ Children's cancer pain seemed even less positively correlated with pathology than adults' cancer pain. Beales suggested that some of the psychological mechanisms involved in pain perception may be manipulated more easily in children than in adults, consistent with our clinical observations that children's cancer pain is more plastic than that of adults.^(1,82) Children seem to possess an enhanced ability to absorb themselves completely in a task, game, or imagined event and thus,

Table 8 Cognitive and behavioural therapies

<i>Cognitive</i>
Information
Choices and control
Supportive counselling
Counselling
Stress management
Attention and distraction
Guided imagery
Hypnosis
<i>Behavioural</i>
Simple exercise
Participation in activities
Desensitization training
Relaxation training
Biofeedback
Behavioural modification

might be more able than adults to trigger endogenous pain-inhibitory mechanisms. Even very young children can easily learn to use a variety of practical pain control methods. The goals of therapy are to enable children to understand what is happening and to have something that they can actively do to lessen their anxiety, distress, and pain.

The specific methods selected depend on the age of the child, the type of pain experienced, and the resources available. Simple methods such as deep breathing, blowing bubbles, alternately tightening and relaxing their fists, squeezing their mother's hand, listening to stories or music, and imagining that they are in a pleasant setting can be very effective for reducing procedural-related pain, when used with appropriate analgesics. When possible, children should learn a few basic methods to reduce their pain and distress. They should not be encouraged to develop a false reliance on the magical benefits of any one method. Instead, they should understand that these practical methods relieve pain because they change the factors that usually increase pain and they help to restore normal sensory input.

All children should learn that pain from some procedures is generally less when they are able to choose the site and rub the area before and after the injection or finger prick. They should learn that pain is less when they are very relaxed. Progressive muscle relaxation with simple exercises in which they tense and relax their body limbs, and biofeedback can help to show them that any type of pain can be intensified if the muscles are always tightened. Children should learn that fear and anxiety can make them tense and increase pain. Then, they need practical tools to alleviate their fear about the cancer or their anxiety towards necessary treatments. Children and families must learn that what they think, how they behave, and how they feel affects their children's pain. Then they can begin to work independently and with staff to create additional non-drug pain control methods based on the child's interest, the cultural setting, and the availability of resources. Specific interventions should be selected and administered to children as part of a comprehensive pain programme, in the same manner as the most appropriate analgesics are selected and administered in adequate doses, at regular dosing intervals, through the most efficient routes.

Summary

Optimal pain control for children in palliative care requires an integrated treatment plan with both drug and non-drug therapies. However, the specific interventions must be selected after determination of the primary and secondary sources of noxious stimulation and after a thorough assessment of the unique situational, behavioural, emotional, and familial factors which affect a child's pain. It is impossible to adequately relieve children's pain from a unidimensional perspective, in which pain is considered as synonymous with the nature and extent of tissue damage. Childhood pain must be viewed from a multidimensional perspective because multiple sensory, environmental, and emotional factors are responsible for the pain—no matter how seemingly clear cut an aetiology. Treatment begins with a thorough assessment of these multiple factors, using structured interviews and standardized measures. Pharmacological, physical, and psychological strategies must be incorporated into a flexible intervention programme for children, in which parents and siblings form an essential component of treatment.

All analgesics should be selected 'by the ladder' and administered 'by the clock', 'by the child', and in an effective and painless route. Dosing intervals should be frequent enough to adequately control pain, so that children do not experience an alternating cycle of pain, drowsy analgesia, pain, etc. Children should also learn some simple pain control strategies so that they can reduce acute pain caused by invasive treatments and disease or therapy related pain. Adjuvant medications should be administered to control aversive symptoms and side-effects. Non-drug therapies should also be used to control pain.

Special problems in pain control may arise when children die at home, unless parents and medical and nursing teams communicate openly about the availability of potent analgesics and the flexibility of dosing routes and regimens. Parents may be unduly anxious because even small children, like

adults with cancer, may require larger opioid doses at more frequent intervals. Parents' fears can lead them to deny the extent to which their children are in pain or children may fail to report pain because they do not want to further distress parents or because they fear injections.

Multiple sources of noxious stimulation are usually responsible for pain in dying children, as the disease progressively affects many systems. Increased disability, toxic side-effects of medication, physical impairment, and the emotional adjustment of children and their families can intensify pain and suffering. Like adults, children's pain affects the entire family and must be viewed within a broader context. Effective pain control is possible when the goals are to reduce or block nociceptive activity by attenuating responses in peripheral afferents and central pathways, activate endogenous pain inhibitory systems, and modify situational factors that exacerbate pain. Thus, the choice for pain control is not merely 'drug versus non-drug therapy', but rather a therapy that mitigates both the causative and contributing factors for pain. Pain management is a continuous dynamic process, since the disease state and factors that influence pain are not static. Different combinations of drug and non-drug therapies will be required at different times. Thus, health professionals must continually assume as much responsibility for monitoring and relieving children's pain as for medically managing their diseases. Children should not suffer. We have the knowledge to ensure that children receive adequate pain control, from the time they are diagnosed to their death. Parents' memories of their children should not be marred by memories that they experienced unrelieved pain.

Acknowledgement

We would like to acknowledge Shue Lin Loo for her excellent assistance in the preparation of this chapter.

References

1. McGrath, P.A. *Pain in Children: Nature, Assessment and Treatment*. New York: Guilford Publications, 1990.
2. Price, D.D. *Psychological Mechanisms of Pain and Analgesia*. Seattle WA: IASP Press, 1999.
3. Casey, K.L. and Bushnell, M.C., ed. *Pain Imaging*. Seattle WA: IASP Press, 2000.
4. McGrath, P.A. and Hillier, L.M. (2002). Modifying the psychologic factors that intensify children's pain and prolong disability. In *Pain in Infants, Children and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), pp. 85–104. Baltimore MD: Lippincott Williams and Wilkins.
5. Schechter, N.L., Berde, C.B., and Yaster, M., ed. *Pain in Infants, Children and Adolescents*, 2nd edn. Baltimore MD: Lippincott Williams and Wilkins, 2002.
6. Ross, D.M. and Ross, S.A. *Childhood Pain: Current Issues, Research, and Management*. Baltimore MD: Urban and Schwarzenberg, 1988.
7. McGrath, P.A. and deVeber, L.L. (1986). The management of acute pain evoked by medical procedures in children with cancer. *Journal of Pain and Symptom Management* 1, 145–50.
8. Chafee, S. (2001). Pediatric palliative care. *Primary Care* 28, 365–90.
9. American Academy of Pediatrics, Committee on Bioethics and Committee on Hospice Care. (2000). Palliative care for children. *Pediatrics* 106, 351–7.
10. Goldman, A. (1998). ABC of palliative care: special problems of children. *British Medical Journal* 316, 49–52.
11. Goldman, A., ed. *Care of the Dying Child*. New York: Oxford University Press, 1994.
12. Goldman, A., Frager, G., and Pometto, M. (2002). Pain and palliative care. In *Pain in Infants, Children and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
13. Frager, G. (1997). Palliative care and terminal care of children. *Child and Adolescent Psychiatric Clinics of North America* 6, 889–90.
14. World Health Organization. *Cancer Pain Relief and Palliative Care in Children*. Geneva: World Health Organization, 1998.

15. Howell, D.A. and Martinson, I.M. (1993). Management of the dying child. In *Principles and Practice of Pediatric Oncology* 2nd edn. (ed. P.A. Pizzo and D.G. Poplack), pp. 1115–24. Philadelphia PA: J.B. Lippincott.
16. Davies, B. and Howell, D. (1998). Special services for children. In *Oxford Textbook of Palliative Medicine* 2nd edn. (ed. D. Doyle, G.W.C. Hanks, and N. MacDonald), pp. 1078–84. Oxford: Oxford University Press.
17. Sourkes, B.M. (1996). The broken heart: anticipatory grief in the child facing death. *Journal of Palliative Care* 12, 56–9.
18. Stevens, M.M. (1998). Care of the dying child and adolescent: family adjustment and support. In *Oxford Textbook of Palliative Medicine* 2nd edn. (ed. D. Doyle, G.W.C. Hanks, and N. MacDonald), pp. 1045–56. Oxford: Oxford University Press.
19. Stevens, M.M. (1998). Psychological adaptation of the dying child. In *Oxford Textbook of Palliative Medicine* 2nd edn. (ed. D. Doyle, G.W.C. Hanks, and N. MacDonald), pp. 1045–56. Oxford: Oxford University Press.
20. McGrath, P.A. and Gillespie, J. (2001). Pain assessment in children and adolescents. In *Handbook of Pain Assessment* 2nd edn. (ed. D.C. Turk and R. Melzack), pp. 97–118. New York: Guilford Press.
21. Finley, G.A. and McGrath, P.J., ed. *Measurement of Pain in Infants and Children*. Seattle WA: IASP Press, 1998.
22. Royal College of Nursing Institute. *Clinical Guideline for the Recognition and Assessment of Acute Pain in Children: Recommendations*. London: Royal College of Nursing Institute, 1999.
23. McGrath, P.J. (1998). Behavioral measures of pain. In *Measurement of Pain in Infants and Children* (ed. G.A. Finley and P.J. McGrath), pp. 83–102. Seattle WA: IASP Press.
24. Sweet, S.D. and McGrath, P.J. (1998). Physiological measures of pain. In *Measurement of Pain in Infants and Children* (ed. G.A. Finley and P.J. McGrath), pp. 59–81. Seattle WA: IASP Press.
25. Hunt, A.M., Goldman, A., Mastroyannopoulou, K., and Seers, K. Identification of pain cues of children with severe neurological impairment. *Proceedings of the 9th World Congress on Pain*. Seattle WA: IASP Press, 1999, Abstract 84.
26. Champion, G.D., Goodenough, B., von Baeyer, C.L., and Thomas, W. (1998). Measurement of pain by self-report. In *Measurement of Pain in Infants and Children* (ed. G.A. Finley and P.J. McGrath), pp. 123–60. Seattle WA: IASP Press.
27. Bush, J.P. and Harkins, S.W., ed. *Children in Pain: Clinical and Research Issues from a Developmental Perspective*. New York: Springer-Verlag, 1991.
28. Gaffney, A., McGrath, P.J., and Dick, B. (2002). Measuring pain in children: developmental and instrumental issues. In *Pain in Infants, Children and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
29. McGrath, P.J. and Unruh, A. *Pain in Children and Adolescents*. Amsterdam: Elsevier, 1987.
30. Peterson, L., Harbeck, C., Farmer, J., and Zink, M. (1991). Developmental contributions to the assessment of children's pain: conceptual and methodological implications. In *Children in Pain: Clinical and Research Issues from a Developmental Perspective* (ed. J.P. Bush and S.W. Harkins), pp. 33–58. New York: Springer-Verlag.
31. Pichard-Leandri, E. and Gauvain-Piquard, A., ed. *La Douleur Chez l'Enfant*. Paris: Medsi/McGraw-Hill, 1989.
32. World Health Organization. *Cancer Pain Relief and Palliative Care*. Geneva: World Health Organization, 1990.
33. Staats, P.S. (1998). Cancer pain: beyond the ladder. *Journal of Back and Musculoskeletal Rehabilitation* 10, 67–80.
34. Galloway, K.S. and Yaster, M. (2000). Pain and symptom control in terminally ill children. *Pediatric Clinics of North America* 47, 711–46.
35. Schechter, N.L., Altman, A., and Weisman, S. (1990). Report of the Consensus Conference on the Management of Pain in Childhood Cancer. *Pediatrics* 86 (Suppl. 5).
36. Acute Pain Management Guideline Panel. *Clinical Practice Guideline: Acute Pain Management in Infants, Children and Adolescents: Operative and Medical Procedures*. Rockville MD: Agency for Health Care Policy and Research, 1992.
37. Consensus Panel. *Pediatric Pain and Symptom Algorithms for Palliative Care*. Seattle WA: Children's Hospital, 1999.
38. Jacox, A. et al. *Management of Cancer Pain. Clinical Practice Guideline*. Rockville MD: Agency for Health Care Policy and Research, US Department of Health and Human Services, Public Health Service, 1994.
39. The Hospital for Sick Children. *Drug Formulary 2001–2002*. Toronto: The Hospital for Sick Children, 2002.
40. Collins, J.J. and Weisman, S.J. (2002). Management of pain in childhood cancer. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
41. Krane, E.J., Leong, M.S., Golianu, B., and Leong, Y.Y. (2002). Treatment of pediatric pain with nonconventional analgesics. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore, MD: Lippincott Williams and Wilkins.
42. Maunukela, E.L. and Olkkola, K.T. (2002). Nonsteroidal anti-inflammatory drugs in pediatric pain management. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
43. Yaster, M., Kost-Byerly, S., and Maxwell, L.G. (2002). Opioid agonists and antagonists. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
44. Yaster, M., Tobin, J.R., and Kost-Byerly, S. (2002). Local anesthetics. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
45. Schutzman, S.A., Liebelt, E., Wisk, M., and Burg, J. (1996). Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine and chlorpromazine for conscious sedation of children undergoing laceration repair. *Annals of Emergency Medicine* 28, 385–90.
46. Dsida, R.M., Avram, M.J., Enders-Klein, C., Maddalozzo, J., and Cote, C.J. (1998). Premedication of pediatric tonsillectomy patients with oral transmucosal fentanyl citrate. *Anesthesia and Analgesia* 86, 66–70.
47. Malviya, S., Voepel-Lewis, T., Huntington, J., Siewert, M., and Green, W. (1997). Effects of anesthetic technique on side effects associated with fentanyl Oralet premedication. *Journal of Clinical Anesthesia* 9, 374–8.
48. Sharar, S.R., Carrougher, G.J., Selzer, K., O'Donnell, F., Vavilala, M.S., and Lee, L.A. (2002). A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *Journal of Burn Care Rehabilitation* 23, 27–31.
49. Gaukroger, P.B. (1993). Patient-controlled analgesia in children. In *Pain in Infants, Children, and Adolescents* (ed. N.L. Schechter, C.B. Berde, and M. Yaster), pp. 203–12. Baltimore MD: Williams and Wilkins.
50. Hill, H.F., Chapman, C.R., Kornell, J.A., Sullivan, K.M., Saeger, L.C., and Bendetti, C. (1990). Self-administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 40, 121–9.
51. Rodgers, B.M., Webb, C.J., Stergios, D., and Newman, B.M. (1988). Patient-controlled analgesia in pediatric surgery. *Journal of Pediatric Surgery* 23, 259–62.
52. Shapiro, B., Cohen, D., and Howe, C. (1991). Use of patient-controlled analgesia for patients with sickle cell disease. *Journal of Pain and Symptom Management* 6, 176.
53. Tahmooressi, J., Schmalzle, S., and Tobin, J. (1991). Patient-controlled analgesia in the adolescent undergoing Cotrel-Dubosset Rod. *Journal of Pain and Symptom Management* 6, 160.
54. Webb, C.J., Paarlberg, J.M., and Sussman, M. (1991). The use of a PCA device by parents or nurses for postoperative pain in children with cerebral palsy. *Journal of Pain and Symptom Management* 6, 160.
55. McDonald, A.J. and Cooper, M.G. (2001). Patient-controlled analgesia: an appropriate method of pain control in children. *Paediatric Drugs* 3, 273–84.
56. McNeely, J.K. and Trentadue, N.C. (1997). Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. *Journal of Pain and Symptom Management* 13, 268–73.
57. Bray, R.J., Woodhams, A.M., Vallis, C.J., Kelly, P.J., and Ward-Platt, M.P. (1996). A double-blind comparison of morphine infusion and patient controlled analgesia in children. *Paediatric Anesthesia* 6, 121–7.
58. Noyes, M. and Irving, H. (2001). The use of transdermal fentanyl in pediatric palliative care. *American Journal of Hospice and Palliative Care* 18, 411–16.

59. Hunt, A., Goldman, A., Devine, T., and Phillips, M. (2001). Transdermal fentanyl for pain relief in a paediatric palliative care population. *Palliative Medicine* **15**, 405–12.
60. Christensen, M.L., Wang, W.C., Harris, S., Eades, S.K., and Wilimas, J.A. (1996). Transdermal fentanyl administration in children and adolescents with sickle cell pain crisis. *Journal of Pediatric Haematology and Oncology* **18**, 372–6.
61. Ahmedzai, S. and Brooks, D. (1997). Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial. *Journal of Pain and Symptom Management* **13**, 254–61.
62. Edinboro, L.E., Poklis, A., Trautman, D., Lowry, S., Backer, R., and Harvey, C.M. (1997). Fatal fentanyl intoxication following excessive transdermal application. *Journal of Forensic Science* **42**, 741–3.
63. Wilder, R.T. (2002). Regional anesthetic techniques for chronic pain management in children. In *Pain in Infants, Children and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
64. Anand, K.J.S., Shapiro, B.S., and Berde, C.B. (1993). Pharmacotherapy with systemic analgesics. In *Pain in Neonates* (ed. K.J.S. Anand and P.J. McGrath), pp. 155–98. New York: Elsevier.
65. Anand, K.J.S. and McGrath, P.J., ed. *Pain in Neonates*. New York: Elsevier, 1993.
66. Fitzgerald, M. and Howard, R. (2002). The neurological basis of pediatric pain. In *Pain in Infants, Children, and Adolescents* 2nd edn. (ed. N.L. Schechter, C.B. Berde, and M. Yaster), Baltimore MD: Lippincott Williams and Wilkins.
67. Franck, L.S. and Gregory, G.A. (1993). Clinical evaluation and treatment of infant pain in the neonatal intensive care unit. In *Pain in Infants, Children, and Adolescents* (ed. N.L. Schechter, C.B. Berde, and M. Yaster), pp. 519–36. Baltimore MD: Williams and Wilkins.
68. Greeley, W.J., Boyd, J.L.L., and Kern, F.H. (1993). Pharmacokinetics of analgesic drugs. In *Pain in Neonates* (ed. K.J.S. Anand and P.J. McGrath), pp. 107–54. Amsterdam: Elsevier.
69. Koren, G., Butt, W., Chinyanga, H., Soldin, S., Tan, Y.K., and Pape, K. (1985). Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *Journal of Pediatrics* **107**, 963–7.
70. Collins, C., Koren, G., Crean, P., Klein, J., Roy, W.L., and MacLeod, S.M. (1985). Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesthesia and Analgesia* **64**, 1078–80.
71. Lynn, S.M. and Slattery, J.T. (1987). Morphine pharmacokinetics in early infancy. *Anesthesiology* **66**, 136–9.
72. *Managing Pain: The Canadian Health Care Professional's Reference*. Healthcare and Financial Publishing, Rogers Media, 2002, pp. 64–6.
73. Spiegelblatt, L., Laine-Ammara, G., Pless, I.B., and Guyver, A. (1994). The use of alternative medicine by children. *Pediatrics* **94**, 811–14.
74. Dahlquist, L.M., Gil, K.M., Armstrong, F.D., Ginsberg, A., and Jones, B. (1985). Behavioural management of children's distress during chemotherapy. *Journal of Behavioural Therapy and Experimental Psychiatry* **16**, 325–9.
75. Dash, J. (1980). Hypnosis for symptom amelioration. In *Psychological Aspects of Childhood Cancer* (ed. J. Kellerman), pp. 215–30. Springfield IL: Charles C. Thomas.
76. Hartman, G.A. (1981). Hypnosis as an adjuvant in the treatment of childhood cancer. In *Living with Childhood Cancer* (ed. J.J. Spinetta and P. Deasy-Spinetta), pp. 143–52. Toronto: C.V. Mosby Co.
77. Hilgard, J.R. and LeBaron, S. (1982). Relief of anxiety and pain in children and adolescents with cancer: quantitative measures and clinical observations. *International Journal of Clinical Experimental Hypnosis* **30**, 417–42.
78. Hilgard, J.R. and LeBaron, S. *Hypnotherapy of Pain in Children with Cancer*. Los Altos CA: William Kaufman, 1984.
79. Jay, S.M., Elliott, C.H., Ozolins, M., Olson, R.A., and Pruitt, S.D. (1985). Behavioural management of children's distress during painful medical procedures. *Behaviour Research and Therapy* **23**, 513–52.
80. Katz, E.R., Kellerman, J., and Ellenberg, L. (1987). Hypnosis in the reduction of acute pain and distress in children with cancer. *Journal of Pediatric Psychology* **12**, 379–94.
81. LaBaw, W.L., Holton, C., Tewell, K., and Eccles, D. (1975). The use of self-hypnosis by children with cancer. *American Journal of Clinical Hypnosis* **17**, 233–8.
82. McGrath, P.A. and Hillier, L.M. (2002). A practical cognitive-behavioral approach for controlling children's pain. In *Psychological Approaches to Pain Management* 2nd edn. (ed. D.C. Turk and R. Gatchel), New York: Guilford Press.
83. Olness, K. (1981). Imagery (self-hypnosis) as adjunct therapy in childhood cancer: clinical experience with 25 patients. *American Journal of Pediatric Hematology/Oncology* **3**, 313–21.
84. Olness, K. (1981). Hypnosis in pediatric practice. *Current Problems in Pediatrics* **12**, 1–47.
85. Zeltzer, L. and LeBaron, S. (1982). Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *Journal of Pediatrics* **101**, 1032–5.
86. Hall, H. (1999). Hypnosis and pediatrics. In *Medical Hypnosis: An Introduction and Clinical Guide* (ed. R. Tennes), pp. 79–93. New York: Churchill Livingstone.
87. LeBaron, S. and Zeltzer, L.K. (1996). Children in pain. In *Hypnosis and Suggestion in the Treatment of Pain* (ed. J. Barber), pp. 305–40. New York: Norton.
88. Olness, K. and Kohen, D.P. *Hypnosis and Hypnotherapy with Children*. New York: Guilford Press, 1996.
89. Beales, J.G. (1979). Pain in children with cancer. In *Advances in Pain Research and Therapy* (ed. J.J. Bonica and V. Ventafridda), pp. 89–98. New York: Raven Press.