25

Pediatric cancer pain

JOHN J COLLINS, MICHAEL M STEVENS, AND CHARLES B BERDE

KEY LEARNING POINTS

- Pain is a common symptom in children with cancer.
- Pediatric cancer pain management should follow the logical, simple guidelines produced by the World Health Organization in combination with knowledge of the individual child and her or his family and an open mind about individual responses to analgesics.
- Most cancer pain in children is due to treatment. Tumor-related pain occurs at diagnosis, at the time of tumor recurrence, and when tumors become treatment resistant. Breakthrough cancer pain in children is usually of sudden onset, severe, and short-lived.
- Most cancer pain in children can be adequately treated.
- A small percentage of children develop intractable pain which is more common in children with solid tumors metastatic to the spinal cord, spinal nerve roots, or large peripheral nerves. In these circumstances, consideration for a rapid opioid dose escalation or nerve block should be given.

INTRODUCTION

The World Health Organization (WHO) developed guidelines for the global application of the principles of pain management and palliative care for children with cancer.[1, 2] The guidelines contain information on pain assessment, the administration of analgesics and adjuvant analgesics, and the application of nonpharmacologic pain interventions as applicable to children with cancer pain.[1, 2] In effect, the WHO has established the principles of pain management and palliative care as a required standard of care for all children with cancer, irrespective of geographic location.

THE ETIOLOGY OF TUMOR-RELATED PAIN

Nociceptors are nerves which receive and transmit painful stimuli. Nociceptors use a diversity of signal transduction mechanisms to detect noxious physiological stimuli, and several of these mechanisms may be involved in driving cancer pain.[3] When nociceptors are exposed to products of tumor cells, tissue injury or inflammation, their excitability is altered and this information is relayed to the spinal cord and then to higher centers in the brain.[3] Some of the mechanisms that appear to be involved in generating and maintaining cancer pain include activation of nociceptors by factors such as extracellular protons,

endothelin-1, interleukins, prostaglandins, and tumor necrosis factor.[3]

THE EPIDEMIOLOGY OF CANCER PAIN IN PEDIATRICS

Pain is a common symptom experienced by children with cancer. As part of the validation study of the Memorial Symptom Assessment Scale 10–18 (MSAS 10–18),[4][V] detailed information was acquired about symptom characteristics from a heterogeneous population of children with cancer aged 10–18 years at Memorial Sloan Kettering Cancer Center, New York. The MSAS 10-18 is a 30-item multidimensional symptom assessment scale that records the prevalence and characteristics of a broad range of physical and psychological symptoms. Children were asked about their symptoms during the preceding week. Pain was the most prevalent symptom in the inpatient group (84.4 percent) and was rated as moderate to severe by 86.8 percent and highly distressing ("quite a bit to very much") by 52.8 percent of these children. Pain was experienced by 35.1 percent of the outpatient group, of whom 75 percent rated it as being moderate to severe and 26.3 percent rated distress as "quite a bit to very much."

A study of children with noncentral nervous system (CNS) malignancies at the National Cancer Institute found that 62 percent presented to their practitioners with complaints of pain prior to the diagnosis of cancer.[5][V] Pain was present for a median of 74 days before definitive treatment was begun. The duration of pain experienced by patients with metastatic disease was not longer than that for patients without distant spread. The majority of children had resolution of pain following the initiation of therapy directed at their cancer. Children with hematological malignancy had a shorter duration of pain following the institution of cancer treatment than those with solid tumor.[5]

Children with brain tumors often present to their practitioners with either symptoms consistent with raised intracranial pressure or abnormal neurological signs.[6] A retrospective review of children with spinal cord tumors showed that most children with spinal cord tumors present with a complaint of pain.[7] Back pain is more common than abnormal neurological signs as a sign of spinal cord compression in children[8] and spinal cord compression due to metastatic disease is more likely to occur late in a child's illness.[8]

Tumor-related pain predominates at diagnosis and during the early phase of treatment for childhood cancer and may recur at the time of relapse or when tumors become resistant to treatment. As multimodality cancer treatment protocols evolve for each patient, treatment-related, rather than tumor-related, causes of pain predominate.[9] Causes of treatment-related pain include mucositis, phantom limb pain, infection, antineoplastic therapy-related pain, postoperative pain, and procedure-related pain (e.g. needle puncture, bone marrow aspiration, lumbar puncture, removal of central venous line).

Tumor-related pain frequently recurs in patients at the time of relapse and during the terminal phase of an illness. Palliative chemotherapy and radiation therapy, depending on tumor type and sensitivity, are sometimes instituted as modalities of pain control in terminal pediatric malignancy. Severe pain in terminal pediatric malignancy occurs more commonly in patients with solid tumors metastatic to spinal nerve roots, nerve plexi, large peripheral nerve, or spinal cord compression.[10]

A variety of chronic pain conditions have been encountered in young adult survivors of childhood cancer as a consequence of cancer treatment.[11] These conditions include chronic regional pain syndrome of the lower extremity, phantom limb pain, avascular necrosis of multiple joints, mechanical pain due to failure of bony union after tumor resection, and postherpetic neuralgia. A proportion of these patients require opioids for the management of their nonmalignant pain.

BREAKTHROUGH CANCER PAIN IN CHILDREN

The prevalence, characteristics, and impact of breakthrough pain in children with cancer have only recently been characterized.[12][V] Twenty-seven pediatric in- and outpatients with cancer (aged 7–18 years) who had severe pain requiring treatment with opioids and who received care in the Oncology Unit at the Children's Hospital at Westmead, Sydney, Australia participated in this study. The children responded to a structured interview designed to characterize breakthrough pain in children. Measures of pain, anxiety, and depressed mood were completed. Fifty-seven percent experienced one or more episodes of breakthrough pain during the preceding 24 hours, each episode lasted seconds to minutes, occurred three to four times per day, and most commonly was characterized as "sharp" and "shooting" by the children. Younger children (7–12 years) had a significantly higher risk of experiencing breakthrough pain compared to teenagers. Although no statistical difference could be shown between children with and without breakthrough pain in regard to anxiety and depression, children with breakthrough pain reported significantly more interpersonal problems on the Child Depression Inventory subtest. The most effective treatment of an episode of breakthrough pain was a patient-controlled analgesia (PCA) opioid bolus dose.

NONPHARMACOLOGICAL METHODS OF PAIN CONTROL IN CHILDREN WITH CANCER

Nonpharmacological methods of pain control in children include a variety of techniques categorized as physical

(e.g. massage, heat and cold stimulation, electrical nerve stimulation, acupuncture), behavioral (e.g. exercise, operant conditioning, relaxation, biofeedback, modeling, desensitization, art and play therapy), or cognitive (e.g. distraction, attention, imagery, thought stopping, hypnosis, music therapy, psychotherapy), according to whether the intervention is focused on modifying an individual's sensory perception, behaviors, or thoughts and coping abilities.[13]

A quiet, calm environment conducive to reducing stress and anxiety, in a location separate from the child's room, is a nonpharmacological strategy arranged prior to performing a medical procedure in a child. Providing a combination of a description of the steps of a given procedure and of the sensations experienced is perhaps the most common intervention for the preparation of children about to undergo invasive medical procedures. Unexpected stress is more anxiety provoking than anticipated or predictable stress.[14]

The choice of which nonpharmacological method to use is based on factors such as the child's age, behavioral factors, coping ability, fear and anxiety, and the type of pain experienced.[13] Cognitive-behavioral techniques are most commonly used in the pediatric cancer patient to decrease distress and enhance a child's ability to cope with medical procedures. The decision to use a psychologic or pharmacologic approach or both depends on the knowledge of the procedure, the skill of the practitioner, the understanding of the child, and the expectations of pain and anxiety for that child undergoing that procedure.[14]

Similarly, the role of distraction techniques in reducing children's distress during procedures has been examined by several investigators and shown to be generally effective. Distraction was less effective for younger children in one study.[15] Another study enlisted the support of parents, and showed not only a reduction in the children's behavioral distress but also lowering of the parent's anxiety.[16] Several investigators have examined and shown the effectiveness of cognitive-behavioral interventions comprising of multiple components, which have included preparatory information, relaxation, imagery, positive coping statements, modeling, and/or behavioral rehearsal.[13, 17, 18] The effectiveness of hypnosis in the reduction of pain and anxiety during bone marrow aspiration and lumbar puncture in children has been confirmed by several reports.[19, 20, 21, 22][V]

PHARMACOLOGICAL MANAGEMENT OF CANCER PAIN IN CHILDREN

Analgesic studies

The need to improve pain management in children with cancer is demonstrated by data which indicate that pain is often not adequately assessed and treated effectively in this population.[23] Improvement in pain management will be dependent not only on advances in pediatric analgesic therapeutics but also on strategies to correct barriers to the adequate treatment of pain in these children. Few analgesic studies have been performed in children with cancer.

The major difficulty in performing analgesic studies in children with cancer relates to the heterogeneous nature of pain in this population. Solid tumors are less common in children than in the adult population and it is less likely that children will have chronic cancer pain due to their tumor. Children often receive therapies directed at the control of their tumors until late in the course of their illnesses. These epidemiological and treatment variables make it less likely that a subpopulation of children with cancer exists that has a chronic stable pattern of pain amenable to evaluation in an analgesic drug trial.

Most analgesic studies performed in children with cancer had small patient numbers, few were controlled studies, and only recently has self-report been used as an outcome measure for the effectiveness of analgesia. There have been no controlled clinical trials of adjuvant analgesic agents in pediatrics. Given the difficulties of performing analgesic studies in children with cancer, pediatric analgesic studies have usually been performed using a postoperative pain model. Although the pharmacokinetic and the major pharmacodynamic properties (analgesia and sedation) of most opioids have been studied in this manner in pediatrics, little information is available about oral bioavailability, potency ratios, and other pharmacodynamic properties.

Analgesics for the management of tumor or treatment-related cancer pain

Analgesics can be divided into three groups of drugs: (1) nonopioid analgesics, (2) opioid analgesics, (3) adjuvant analgesics. The prescription of these drugs for children with cancer pain is based on the WHO analgesic ladder which emphasizes pain intensity as the guide to choice of analgesic, rather than etiologic factors. In other words, the prescription of analgesics should be according to pain severity, ranging from acetaminophen and nonsteroidal anti-inflammatory drugs (NSAID) for mild pain to opioids for moderate to severe pain. The choice of analgesics is individualized to achieve an optimum balance between analgesia and side effects (see Part II, Drug therapies for cancer pain).

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is one of the most commonly used nonopioid analgesics in children with cancer. It has a potential for hepatic and renal injury[24] but this is uncommon in therapeutic doses. Unlike aspirin, paracetamol does not have an association with Reye

syndrome. The antipyretic action of paracetamol may be contraindicated in neutropenic patients in whom it is important to monitor fever. Pediatric dosing of paracetamol has been based on the antipyretic dose–response. Oral dosing of 15 mg/kg every four to six hours is recommended, with a maximum daily dose of 60 mg/kg/day for patients of normal or average build.

No data are available on the safety of chronic paracetamol administration in children. In Australia, New South Wales Health Policy mandates that paracetamol should not be administered to children for more than 48 hours without a medical review.[25][V] Intravenous paracetamol is available as a therapeutic analgesic option in some countries. Its use has been documented in the context of pediatric postoperative pain management[26] and practice guidelines are evolving.[27]

ACETYLSALICYLIC ACID (ASPIRIN) AND NSAIDS

Acetylsalicylic acid and NSAIDs are frequently contraindicated in pediatric oncology patients who are often at risk from bleeding due to thrombocytopenia. In a comparative study of acetylsalicylic acid and ibuprofen in children with juvenile rheumatoid arthritis, the drugs were equally efficacious, but the drop-out rate caused by side effects was significantly higher in the aspirin group.

Choline magnesium trisalicylate (Trilisate®) has been widely recommended because of reports in adults of minimal effects on platelet function *in vitro* and experimental studies showing minimal gastric irritation in rats, in contrast to acetylsalicylic acid.[28] The studies do not include medically frail patients with thrombocytopenia or other morbidities.

The cyclooxygenase-2 (COX-2) inhibitors target a specific isoenzyme involved in the generation of prostanoids, which contribute to pain and inflammation. Whilst celecoxib and meloxicam have undergone some limited trials in children with rheumatoid arthritis and postoperative pain,[29, 30] their role in pediatric pain management is unclear. Rofecoxib was removed from the international market because of increased risk of cardiovascular events in adults.[31]

CODEINE

In pediatrics, codeine is commonly administered via the oral route and often administered in combination with paracetamol. It is prescribed for mild to moderate pain. Codeine is typically administered in pediatrics in oral doses of 0.5–1 mg/kg every four hours for children over six months of age. Pharmacogenetic studies have demonstrated that 4–14 percent of the population lack the hepatic enzyme responsible for the conversion of codeine to morphine. A pediatric study has shown that 35 percent of children showed inadequate conversion of codeine to morphine.[32] The prescription of codeine as an analgesic in pediatrics is declining.

TRAMADOL

Tramadol may be a useful analgesic for the management of moderate cancer pain and is thought to cause less respiratory depression than morphine. Few data exist on the safety and efficacy of tramadol in patients less than 16 years of age.

OXYCODONE

Oxycodone is used for moderate to severe pain in children with cancer. Oxycodone may be available only as an oral preparation in combination with paracetamol in some countries. The total daily paracetamol dose may be the limiting factor in dose escalation of these products. Oxycodone has a higher clearance value and a shorter elimination half-life ($t_{1/2}$) in children aged 2–20 years than adults.[33, 34] Oxycodone is available as a long-acting preparation in some countries.

MORPHINE

Morphine is one of the most widely used opioids for moderate to severe cancer pain in children. Evolving data indicate that a variable human analgesic response to morphine may be explained, in part, by genetic variation and different μ-opioid receptor neurotransmitter responses.[35]

The binding of morphine to plasma protein is age-dependent. In premature infants, less than 20 percent is bound to plasma proteins.[36, 37] Within the neonatal period for term infants, the volume of distribution is linearly related to age and body surface area,[36, 37, 38] but after the neonatal period the values are approximately the same as adults.[39, 40]

Morphine clearance is delayed in the first one to three months of life. The half-life of morphine ($t_{1/2}$) changes from values of 10–20 hours in preterm infants to values of one to two hours in preschool children.[39, 40] Therefore, starting doses in very young infants should be reduced to approximately 25–30 percent on a per kilogram basis relative to dosing recommended for older children.

Following oral dosing, morphine has a significant first pass metabolism in the liver. An oral to parenteral potency ratio of approximately 3:1 is commonly encountered during chronic administration.[41] A typical starting dose for immediate release oral morphine in opioid-naive children is 0.3 mg/kg every four hours. Typical starting intravenous infusion rates are 0.02–0.03 mg/kg per hour beyond the first three months of life, and 0.015 mg/kg per hour in younger infants. Sustained release preparations of morphine are available for children and permit oral dosing at intervals of either twice or three times daily. Crushing sustained released tablets produces immediate release of morphine. This limits their use in children who must chew tablets.

HYDROMORPHONE

Hydromorphone is an alternative opioid when the dose escalation of morphine is limited by side effects. Hydromorphone is available for oral, intravenous, subcutaneous, epidural, and intrathecal administration. Adult studies indicate that intravenous hydromorphone is five to eight times as potent as morphine. A double-blinded randomized cross-over comparison of morphine to hydromorphone using PCA in children and adolescents with mucositis following bone marrow transplantation showed that hydromorphone was well tolerated and had a potency ratio of approximately 6:1 relative to morphine in this setting.[42][II] Because of its high potency and aqueous solubility, hydromorphone is convenient for subcutaneous infusion. Little is known about the pharmacokinetics of hydromorphone in infants.

FENTANYL

Fentanyl is a synthetic opioid which is approximately 50–100 times more potent than morphine during acute intravenous administration. The half-life of this opioid is prolonged in preterm infants undergoing cardiac surgery,[43] but comparable values with those of adults are reached within the first months of life.[44, 45, 46, 47] The clearance of fentanyl appears to be higher in infants and young children than in adults.[46, 47] Fentanyl may also be used for continuous infusion for selected patients with dose-limiting side effects from morphine. Rapid administration of high doses of intravenous (i.v.) fentanyl may result in chest wall rigidity and severe ventilatory difficulty.

Oral transmucosal fentanyl produces a rapid onset of effect and escapes first-pass hepatic clearance. Schechter *et al.*[48][V] described the use of oral transmucosal fentanyl for sedation/analgesia during bone marrow biopsy/aspiration and lumbar puncture. This formulation was safe and effective, although the frequency of vomiting may be a limiting factor in its tolerability. Its use for breakthrough cancer pain in adults has been described.[49]

In a small study utilizing a clinical protocol, the utility, feasibility, and tolerability of transdermal fentanyl was demonstrated in children with cancer pain.[50][V] The mean clearance and volume of distribution of transdermal fentanyl are the same for both adults and children, but the variability is higher in adults.[50] A subsequent larger study confirmed the effectiveness of this analgesic for children.[51][V]

PETHIDINE (MEPERIDINE)

Pethidine has been used for procedural and postoperative pain in children. It is a short half-life synthetic opioid. Neonates have a slower elimination of pethidine than children and young infants.[52, 53, 54, 55, 56] Normeperidine is the major metabolite of pethidine. This can cause CNS excitatory effects, including tremors and convulsions,[57] particularly in patients with impaired renal clearance. Pethidine is therefore not generally recommended for children with chronic pain, but may be an acceptable alternative to fentanyl for short painful procedures.

METHADONE

Methadone is a synthetic opioid which has a long and variable half-life. Following single parenteral doses, its potency is similar to that of morphine. In children receiving postoperative analgesia, methadone produced more prolonged analgesia than morphine.[58, 59] Due to its prolonged half-life, methadone has a risk of delayed sedation and over-dosage occurring several days after initiating treatment.

The oral:parenteral potency ratio is approximately 2:1. Frequent patient assessment is the key to safe and effective use of methadone. If a patient becomes comfortable after initial doses, the dose should be reduced or the interval extended to reduce the likelihood of subsequent somnolence. If a patient becomes oversedated early in dose escalation, it is recommended to stop dosing, not just reduce the dose, and to observe the patient until there is increased alertness. Although "as needed" dosing is discouraged for most patients with cancer pain, some clinicians find this approach a useful way to establish a dosing schedule for methadone.[58, 59] Methadone remains a long-acting agent when administered either as an elixir or as crushed tablets.

Routes and methods of analgesic administration

ORAL

Oral administration of analgesics is the first choice for the majority of children and young patients. Analgesics should generally be administered to children by the simplest, safest, most effective, and least painful route. Oral dosing is generally predictable, inexpensive, and does not require invasive procedures or technologies.

TOPICAL

The eutectic mixture of local anesthetics (EMLA®) is a topical preparation which provides local anesthesia to the skin, dermis, and subcutaneous tissues if applied under an occlusive dressing for at least one hour. It has been shown to be useful for procedural pain, including lumbar puncture[60] and central venous port access[61] in children with cancer. Preliminary studies of topical amethocaine for percutaneous analgesia prior to venous cannulation in children have demonstrated promising safety and efficacy

data.[62] The newer generation of topical local anesthetics promise a quicker onset of action and are currently being reviewed.[63]

INTRAVENOUS

Intravenous administration has the advantage of rapid onset of analgesia, easier opioid dose titration, bioavailability, and continuous effect when infusions are used. The intravenous route of administration is often an option in children with cancer since many have indwelling intravenous access.

SUBCUTANEOUS

The subcutaneous route is an alternative route of administration for children with either no or poor intravenous access. Solutions are generally concentrated so that infusion rates do not exceed 1–3 mL/hour.[64] An application of a topical local anestheic agent is recommended prior to the placement of a subcutaneous needle. A small catheter or butterfly needle (27 gauge) may be placed under the skin of the thorax, abdomen, or thigh and sites changed approximately every three days.

INTRAMUSCULAR

Intramuscular administration is painful and may lead to the underreporting of pain. This route of administration does not permit easy dose titration or infusion and should be avoided.

RECTAL

Rectal administration is discouraged in the pediatric cancer population because of concern regarding infection and because of the great variability of rectal absorption of morphine.[65] Nevertheless, this route of administration may be useful in the home care of the dying child when no other route is available. Slow release morphine tablets can be administered via the rectum.

PCA

PCA is a method of opioid administration that permits the patient to self-administer small bolus doses of opioid within set time limits. PCA caters to an individual's variation in pharmacokinetics, pharmacodynamics, and pain intensity. PCA allows appropriate children to have control over their analgesia and allows them to choose a balance between the benefits of analgesia versus the side effects of opioids. In patients with severe mucositis, for example, opioid dosing can be timed with routine mouth care and other causes of incidental mouth pain. In postoperative use, PCA is widely used successfully by children aged six to seven and above.

PCA has been used successfully for the management of prolonged oropharyngeal mucositis pain following bone marrow transplantation in children and adolescents.[42, 66, 67][II] A controlled comparison of staff-controlled continuous infusion (CI) of morphine and PCA in adolescents with severe oropharyngeal mucositis found that the PCA group had equivalent analgesia but less sedation and less difficulty concentrating.[66][II]

Opioid dose schedules

Unless a child's episodes of pain are truly incidental and unpredictable, analgesics should be administered at regular times to prevent breakthrough pain. "Rescues" are supplemental "as needed" doses of opioid incorporated into the analgesic regimen to allow a patient to have additional analgesia should breakthrough pain occur. Rescue doses of opioid may be calculated as approximately 5–10 percent of the total daily opioid requirement and may be administered every hour.[41]

Opioid dose escalation may be required after opioid administration begins and periodically thereafter. The size of a dose increment may be calculated as follows.

- If greater than approximately six "rescue" doses of opioid are given in a 24-hour period, then the total daily opioid dose should be increased by the total of opioid given as "rescue" medication. For example, the hourly average of the total daily rescue opioid should be added to the baseline opioid infusion. An alternative to this method would be to increase the baseline infusion by 50 percent.[41]
- "Rescue" doses are kept as a proportion of the baseline opioid dose. This dose can be 5–10 percent of the total daily dose.[41] An alternative guideline for opioid infusions is between 50 and 200 percent of the hourly basal infusion rate (see **Box 25.1**).[41]

Opioid switching

The usual indication for switching to an alternative opioid is dose-limiting toxicity. This approach is recommended by the observation that a switch from one opioid to another is often accompanied by change in the balance between analgesia and side effects.[68] A favorable change in opioid analgesia to side effect profile may be experienced if there is less cross-tolerance at the opioid receptors mediating analgesia than at those mediating adverse effects.[69]

Following a prolonged period of regular dosing with one opioid, equivalent analgesia may be attained with a dose of a second opioid that is smaller than that calculated from an equianalgesic table, as shown in **Table 25.1.**[69] An opioid switch is usually accompanied by a reduction in the equianalgesic dose (approximately 50

Box 25.1 Case examples for opioid dose calculation and dose escalation

A four-year-old girl, weighing 20 kg has severe continuous pain related to metastatic neuroblastoma. What is an appropriate opioid dose schedule?

Due to the continuous nature of this patient's pain, an appropriate schedule would be to provide either regular dosing via the oral route, or, alternatively, a continuous intravenous infusion should be started. In addition, to account for additional or "breakthrough" pain, the regime should have supplementary opioid to be given when required.

OPTIONS

The oral dose of morphine is 0.3 mg/kg every four hours (i.e. 6 mg po every four hours) using immediate release morphine (IRM). An appropriate "breakthrough" dose would be 3.5 mg IRM every hour (i.e. the total daily opioid dose is 36 mg, 10 percent of this dose is approximately 3.5 mg morphine). If this regime seems satisfactory with time, it may be reasonable to switch from IRM to slow release morphine (SRM). An appropriate regime would be 15 mg SRM twice a day. The "breakthrough" IRM dose remains the same.

As an alternative, a loading dose of intravenous morphine (0.1 mg/kg) could be given, followed by starting a morphine infusion of 0.02 mg/kg per hour (= 0.4 mg per hour morphine). An appropriate "breakthrough" dose could be 0.4 mg i.v. every hour.

During the next 24 hours, six additional "breakthrough" doses of oral morphine were given. How should the opioid regime be changed?

An additional 21 mg of oral morphine was given as "breakthrough" dosing (i.e. 6×3.5 mg = 21 mg). This dose could be divided and be given as additional SRM. An appropriate new regime could be 25 mg SRM twice a day. The total daily dose of morphine is now 50 mg, an appropriate "breakthrough" dose of IRM would now be 5 mg.

percent for short half-life opioids). In contrast to short half-life opioids, the doses of methadone required for equivalent analgesia after switching may be of the order of 10–20 percent of the equianalgesic dose of the previously used short half-life opioid. A protocol for methadone dose conversion and titration has been documented for adults.[70] The basis of this dose reduction is because of the *d*-methadone effect as an antagonist at the *N*-methyl-D-aspartic acid (NMDA) receptor.

A retrospective study was performed to determine the therapeutic value of opioid rotation in a large pediatric oncology center.[71][V] Fourteen percent of children receiving opioid therapy had 30 opioid rotations. Mucositis was the major cause of pain. The opioid was rotated either for excessive side effects with adequate analgesia (70 percent), excessive side effects with inadequate analgesia (16.7 percent), or tolerance (6.7 percent). Adverse opioid effects were resolved in 90 percent of cases, all failures occurred when morphine was rotated to fentanyl. There was no significant loss of pain control or increase in mean morphine equivalent dose requirements. Opioid rotation had a positive impact on managing dose-limiting side effects of, or tolerance to, opioid therapy during cancer pain treatment in children. This was accomplished without loss of pain control or having to significantly increase the dose of opioid therapy.[71]

Opioid side effects

All opioids can potentially cause the same constellation of side effects. Children do not necessarily report side effects voluntarily (e.g. constipation, pruritus, dreams) and should be asked specifically about these problems. An assessment of opioid side effects is included in an assessment of analgesic effectiveness. If opioid side effects limit opioid dose escalation, then consideration should be given to an opioid switch. Tolerance to some opioid side effects (e.g. sedation, nausea and vomiting, pruritus) often develops within the first week of starting opioids. Children do not develop tolerance to constipation as an opioid side effect and concurrent treatment with laxatives should always be considered (see **Table 25.2**).

Adjuvant analgesics

Adjuvant analgesics are a heterogeneous group of drugs that have a primary indication other than pain but are analgesic in some painful conditions.[72] Adjuvant analgesics are commonly, but not always, prescribed with primary analgesic drugs. Common classes of these agents include antidepressants, anticonvulsants, neuroleptics, psychostimulants, antihistamines, corticosteroids, and centrally acting skeletal muscle relaxants.

ANTIDEPRESSANTS

Data from adult studies have guided the use of antidepressants as adjuvant analgesics in pediatrics. Tricyclic antidepressants have been used for a variety of pain conditions in adults, including postherpetic neuralgia,[73]

Table 25.1 Opioid analgesic initial dosage guidelines.

Drug	Equianalgesic doses		Usual starting i.v. or s.c. doses and intervals		Parenteral/oral dose ratio	Usual starting oral doses and intervals	
	Parenteral	Oral	Child $<$ 50 kg	Child $>$ 50 kg		Child $<$ 50 kg	Child $>$ 50 kg
Codeine	120 mg	200 mg	NR	NR	1:2	0.5–1.0 mg/kg q 3–4	30-60 mg q 3-4
Morphine	10 mg	30 mg (chronic)	Bolus: 0.1 mg/kg q 2–4 h	Bolus 5–8 mg q 2–4 h	1:3 (chronic)	Immediate release: 0.3 mg/kg q 3–4 h	Immediate release: 15–20 mg q 3–4 h
			Infusion 0.03 mg/kg/h	Infusion 1 mg/h	1:6 (single dose)	Sustained release: 20–35 kg: 10–15 mg q 8–12 h 35–50 kg: 15–30 mg q 8–12 h	Sustained release: 30–45 mg q 8–12 h
Oxycodone	NA	15 mg	NA	NA	NA	0.1–0.2 mg/kg q 3–3 h	5–10 mg q 3–4 h
Methadone[a]	10 mg	10 mg	0.1 mg/kg q 4–8 h	1:2	1:1.5–1:2	0.15–0.2 mg/kg q 4–8 h	7–10 mg q 4–8 h
Fentanyl	100 μg (0.1 mg)	NA	Bolus: 0.5–1.0 μg/kg q 1–2 h Infusion: 0.5–2.0 μg/kg/h	Bolus: 25–50 μg q 1–2 h Infusion 25–100 μg/h	NA	NA	NA
Hydromorphone	1.5–2.0 mg	6–8 mg	Bolus: 0.02 mg q 2–4 h Infusion: 0.06 mg/kg/h	Bolus: 1 mg q 2–4 h Infusion: 0.3 mg/h	1:4	0.04–0.09 mg/kg q 3–4 h	2–4 mg q 3–4 h
Meperidine[b] (pethidine)	75–100 mg	300 mg	Bolus: 0.8–1.0 mg/kg q 2–3 h	Bolus: 50–75 mg q 2–3 h	1:4	2–3 mg/kg q 3–4 h	100–150 mg q 3–4 h

[a]Methadone requires additional vigilance, because it can accumulate and produce delayed sedation. If sedation occurs, doses should be withheld until sedation resolves. Thereafter, doses should be substantially reduced or the dosing interval should be extended to 8–12 hours (or both).

[b]Meperidine should be generally avoided if other opioids are available, especially with chronic use, because its metabolite can cause seizures.

NA, not available; NR, not recommended.

Note: Doses refer to patients older than six months. In infants younger than six months, initial doses per kilogram should begin at approximately 25 percent of the doses per kilogram recommended here. All doses are approximate and should be adjusted according to clinical circumstances. Reprinted from Berde CB, Billett AL, Collins JJ. Symptom management in supportive care. In: Pizzo PA, Poplack DG (eds). *Principles and practice of pediatric oncology*, 5th edn. 2006, with permission from Lippincott Williams and Wilkins.

Table 25.2 Management of opioid side effects.

Side effect	Treatment
Constipation	1. Regular use of stimulant and stool softener laxatives (fiber, fruit juices are often insufficient) 2. Ensure adequate water intake
Sedation	1. If analgesia is adequate, try dose reduction 2. Unless contraindicated, add nonsedating analgesics, such as acetaminophen or NSAIDs, and reduce opioid dosing as tolerated 3. If sedation persists, try methylphenidate or dextroamphetamine 0.05–0.2 mg/kg po b.i.d. in early am and midday 4. Consider an opioid switch
Nausea	1. Exclude disease processes (e.g. bowel obstruction, increased intracranial pressure) 2. Antiemetics (phenothiazines, ondansetron, hydroxyzine) 3. Consider an opioid switch
Urinary retention	1. Exclude disease processes (e.g. bladder neck obstruction by tumor, impending cord compression, hypovolemia, renal failure, etc.) 2. Avoid other drugs with anticholinergic effects (e.g. tricyclics, antihistamines) 3. Consider short-term use of bethanechol or Crede maneuver 4. Consider short-term catheterization 5. Consider opioid dose reduction if analgesia adequate or an opioid switch if analgesia inadequate
Pruritus	1. Exclude other causes (e.g. drug allergy, cholestasis) 2. Antihistamines (e.g. diphenhydramine hydroxyzine) 3. Consider an opioid dose reduction if analgesia adequate, or an opioid switch. Fentanyl causes less histamine release
Respiratory depression:	
Mild–moderate	1. Awaken, encourage to breathe 2. Apply oxygen 3. Withhold opioid dosing until breathing improves, reduce subsequent dosing by at least 25%
Severe	1. Awaken if possible, apply oxygen, assist respiration by bag and mask as needed 2. Titrate small doses of naloxone (0.02 mg/kg increments as needed), stop when respiratory rate increases to 8–10/min in older children or 12–16/min in infants, do not try to awaken fully with naloxone ****Do not give a bolus dose of naloxone as severe pain and symptoms of opioid withdrawal may ensue**** 3. Consider a low-dose naloxone infusion or repeated incremental dosing 4. Consider short-term intubation in occasional cases where risk of aspiration is high
Dysphoria/confusion/ hallucinations	1. Exclude other pathology as a cause for these symptoms before attributing them to opioids 2. When other causes excluded, change to another opioid 3. Consider adding a neuroleptic such as haloperidol (0.01–0.1 mg/kg po/i.v. every 8 hours to a maximum dose of 30 mg/day)
Myoclonus	1. Usually seen in the setting of high-dose opioids, or alternatively, rapid dose escalation 2. No treatment may be warranted, if this is infrequent and not distressing to the child 3. Consider an opioid switch or treat with clonezepam (0.01 mg/kg po every 12 hours to a maximum dose of 0.5 mg/dose) or a parenteral benzodiazepine (e.g. diazepam) if the oral route is not tolerated

Reprinted from Berde CB, Billett AL, Collins JJ. Symptom management in supportive care. In: Pizzo PA, Poplack DG (eds). *Principles and Practice of Pediatric Oncology*, 5th edn. 2006, with permission from Lippincott Williams and Wilkins.

[II] diabetic neuropathy,[74][II] tension headache,[75] migraine headache,[76] rheumatoid arthritis,[77] chronic low back pain,[78] and cancer pain.[79] Antidepressants are effective in relieving neuropathic pain. With very similar results for anticonvulsants it is still unclear which drug class should be the first choice.[80]

Baseline hematology and biochemistry tests (including liver function tests) and an electrocardiogram (ECG) to exclude Wolff–Parkinson–White syndrome or other cardiac conduction defects have been recommended prior to starting treatment with tricyclic antidepressants.[81] The measurement of antidepressant plasma concentration allows confirmation of compliance and ensures that optimization of dosage has occurred before discontinuing. An ECG is recommended periodically during long-term use, or if standard milligrams per kilogram dosages are exceeded.[82]

PSYCHOSTIMULANTS

Dextroamphetamine potentiates opioid analgesia in postoperative adult patients[83] and methylphenidate

counteracts opioid-induced sedation[84] and cognitive dysfunction[85] in advanced cancer patients. Psychostimulants may allow dose escalation of opioids in patients who have somnolence as a dose-limiting side effect.[72] The potential side effects of methylphenidate include anorexia, insomnia, and dysphoria. The use of dexamfetamine (dextroamphetamine) and methylphenidate was reported in a retrospective survey of 11 children receiving opioids for a variety of indications, including cancer pain.[86] Somnolence was reduced in these patients without significant adverse side effects.

CORTICOSTEROIDS

Corticosteroids may produce analgesia by a variety of mechanisms, including anti-inflammatory effects, reduction of tumor edema, and, potentially by a reduction of spontaneous discharge in injured nerves.[87] Dexamethasone tends to be used most frequently because of its high potency, longer duration of action, and minimal mineralocorticoid effect. Corticosteroids may have a role in bone pain due to metastatic bone disease,[88] cerebral edema due to either primary or metastatic tumor,[89] or epidural spinal cord compression.[90]

ANTICONVULSANTS

The mechanism of action of anticonvulsants in controlling lancinating pain is not known but is probably related to reducing paroxysmal discharges of central and peripheral neurons. Anticonvulsants are effective in relieving neuropathic pain. With very similar results for antidepressants, it is still unclear which drug class should be the first choice.[80] The use of phenytoin, carbamazepine, and valproate may be problematic in the pediatric cancer population due to their potential adverse effects on the hematological profile. Gabapentin is well tolerated and appears to have a benign efficacy to toxicity ratio in children[91] and may be useful for the treatment of neuropathic pain.

RADIONUCLIDES

The use of other radionuclides for painful osseous metastases has been reported in the adult literature.[92] One pediatric case report indicates the potential role of [131]iodine-metaiodobenylguanidine ([131I]MIBG) for painful metastatic bone disease due to neuroblastoma.[93] The side effects of [131I]MIBG were thrombocytopenia and cystitis.

NEUROLEPTICS

Methotrimeprazine, a phenothiazine, has been reported as being analgesic in the setting of adult cancer pain.[94] Methotrimeprazine is not considered to be a substitute for opioid analgesia. The mechanism by which methotrimeprazine produces analgesia and its role as an adjuvant agent in pediatric cancer pain is unclear. It may be useful as an adjuvant analgesic in a patient with disseminated cancer who experiences pain associated with anxiety, restlessness, or nausea.[72]

ANESTHETIC APPROACHES TO PAIN MANAGEMENT

The use of epidural or subarachnoid infusion in children for cancer pain management is rare, since the majority of pediatric cancer pain is well managed by the methods outlined above.[95] Frequently, by the time these modalities of pain control are considered, relative or absolute contraindications to their use have occurred (e.g. infection or thrombocytopenia, etc.). Anesthetic approaches are usually confined to patients who have pain not responsive to the more common methods of pain control. Anesthetic approaches are more likely to be successful for patients with their most severe pain in a specific region of the body below the neck. Specialists with experience in pediatric regional anesthesia and cancer pain management should be consulted if anesthetic techniques are being considered.[11]

TERMINAL SEDATION

The use of sedation to reduce conscious awareness in the setting of intractable symptom management is rare in pediatrics.[10] Guidelines for the evaluation and treatment of patients with intractable symptoms has been described previously.[96] There is no consensus regarding best practice for sedative prescription in this setting, which should be only considered in the setting of intractable pain or other symptom management. The prescription of terminal sedation should only be made by senior clinicains highly skilled in the symptom management of children.

Although the NMDA antagonist ketamine is commonly administered as a sedative or anesthetic agent, it has been used in a lower dose range as an analgesic for patients with refractory pain. Infusions in a dose range up to 0.2 mg/kg per hour can provide helpful analgesia and generally do not produce dissociation or unconsciousness.

TOLERANCE, PHYSICAL DEPENDENCE, ADDICTION

Analgesic tolerance refers to the progressive decline in potency of an opioid with continued use, so that increasingly higher doses are required to achieve the same analgesic effect. Patients and parents are often reluctant to

increase dosing because of a fear that tolerance will make opioids ineffective at a later date. Parents should be reassured that tolerance in the majority of cases can be managed by simple dose escalation, use of adjunctive medications, or perhaps by opioid switching in the setting of dose-limiting side effects. Clinically relevant pharmacological tolerance is not usually an issue in cancer pain management.

There are some data to suggest that younger patients may be more prone to develop analgesic tolerance. This has been verified in rat studies, indicating that morphine tolerance occurs in younger rats. The notion has been verified in adult studies, indicating that age is an important variable in opioid dose escalation.[97, 98]

Physical dependence is a physiologic state induced after dose reduction or discontinuation of an opioid, or administration of an opioid antagonist. Initial manifestations of withdrawal include yawning, diaphoresis, lacrimation, coryza, and tachycardia. Patients with cancer who have received opioids over a long period of time and in whom it is appropriate to either stop or reduce opioids, should have the opioid dose reduced slowly.

Addiction is a psychological and behavioral syndrome characterized by drug craving and aberrant drug use. Some parents may fear that an exposure to opioids will result in their child subsequently becoming a drug addict. The incidence of opioid addiction was examined prospectively in 12,000 hospitalized adult patients who received at least one dose of a strong opioid.[99] There were only four documented cases of subsequent addiction in patients without a prior history of drug abuse. These data suggest that iatrogenic opioid addiction is an exceedingly uncommon problem, an observation consistent with a large worldwide experience with opioid treatment of cancer pain.

REFERENCES

1. McGrath PA. Development of the World Health Organization Guidelines on cancer pain relief and palliative care in children. *Journal of Pain and Symptom Management*. 1996; **12**: 87–92.
2. ∗ World Health Organization. *Cancer pain relief and palliative care in children*. Geneva: WHO, 1998.
3. Mantyh PW. Cancer pain: causes, consequences and therapeutic opportunities. In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's textbook of pain*. London: Elsevier Churchill Livingstone, 2006: 1087–97.
4. ∗ Collins JJ, Byrnes ME, Dunkel I *et al*. The Memorial Symptom Assessment Scale (MSAS): validation study in children aged 10–18. *Journal of Pain and Symptom Management*. 2000; **19**: 363–7.
5. ∗ Miser AW, McCalla J, Dothage P *et al*. Pain as a presenting symptom in children and young adults with newly diagnosed malignancy. *Pain*. 1987; **29**: 363–77.
6. Blaney SM, Kun LE, Hunter J *et al*. Tumors of the central nervous system. In: Pizzo PA, Poplack DG (eds). *Principles and practice of pediatric oncology*, 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2006: 786–864.
7. Hahn YS, McLone DG. Pain in children with spinal cord tumors. *Child's Brain*. 1984; **11**: 36–46.
8. Lewis D, Packer R, Raney B *et al*. Incidence, presentation, and outcome of spinal cord disease in children with systemic cancer. *Pediatrics*. 1986; **78**: 438–43.
9. Miser AW, Dothage P, Wesley RA *et al*. The prevalence of pain in a pediatric and young adult population. *Pain*. 1987; **29**: 265–6.
10. ∗ Collins JJ, Grier HE, Kinney HC, Berde CB. Control of severe pain in terminal pediatric malignancy. *Journal of Pediatrics*. 1995; **126**: 653–7.
11. Berde CB, Billett A, Collins JJ. Symptom management in supportive care. In: Pizzo PA, Poplack DG (eds). *Principles and practice of pediatric oncology*, 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2006: 1348–79.
12. Friedrichsdorf S, Finney D, Bergin M *et al*. Breakthrough pain in children with cancer. *Journal of Pain and Symptom Management*. 2007; **34**: 209–16.
13. McGrath PA, DeVeber LL. The management of acute pain evoked by medical procedures in children with cancer. *Journal of Pain and Symptom Management*. 1986; **1**: 145–50.
14. Zeltzer L, Jay S, Fisher D. The management of pain associated with pediatric procedures. In: Schechter NL (ed.). *The pediatric clinics of North America*. Philadelphia: W.B. Saunder Company, 1989: 914–64.
15. Kuttner L, Bowman M, Teasdale M. Psychological treatment of distress, pain and anxiety for children with cancer. *Journal of Developmental and Behavioral Pediatrics*. 1988; **9**: 374–81.
16. Manne SL, Redd WH, Jacobsen P *et al*. Behavioral intervention to reduce child and parent distress during venipuncture. *Journal of Consulting and Clinical Psychology*. 1990; **58**: 565–72.
17. Manne SL, Bakeman R, Jacobsen P *et al*. Adult and child interaction during invasive medical procedures: sequential analysis. *Health Psychology*. 1992; **11**: 241–9.
18. Jay SM, Elliott C, Ozolins M *et al*. Behavioral management of children's distress during painful medical procedures. *Behaviour Research and Therapy*. 1985; **5**: 513–20.
19. Katz E, Kellerman J, Ellenberg L. Hypnosis in the reduction of acute pain and distress in children with cancer. *Journal of Pediatric Psychology*. 1987; **12**: 379–94.
20. Hilgard J, LeBaron S. Relief of anxiety and pain in children and adolescents with cancer: quantitative measures and clinical observations. *International Journal of Clinical and Experimental Hypnosis*. 1982; **30**: 417–42.
21. Kellerman J, Zeltzer L, Ellenberg L, Dash J. Adolescents with cancer: hypnosis for the reduction of the acute pain and anxiety associated with medical procedures. *Journal of Adolescent Health Care*. 1983; **4**: 85–90.
22. Zeltzer L, LeBaron S. Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful

procedures in children and adolescents with cancer. *Journal of Pediatrics*. 1982; **101**: 1032–5.

* 23. Ljungman G, Kreugar A, Gordh T *et al*. Treatment of pain in pediatric oncology: a Swedish nationwide survey. *Pain*. 1996; **68**: 385–94.
24. Sandler DP, Smith JC, Weinberg CR *et al*. Analgesic use and chronic renal disease. *New England Journal of Medicine*. 1989; **320**: 1238–43.
25. NSW Health. Paracetamol use. 2006. Available from: www.health.nsw.gov.au/policies/pd/2006/PD2006_004.html.
* 26. Wurthwein G, Koling S, Reich A *et al*. Pharmacokinetics of intravenous paracetamol in children and adolescents under major surgery. *European Journal of Clinical Pharmacology*. 2005; **60**: 883–8.
27. NSW Therapeutic Advisory Group Inc. IV paracetamol – where does it sit in hospital practice? 2005. NSW, Australia. Current Opinion. Available from: www.ciap.health.nsw.gov.au/nswtag/publications/posstats/ivparacetamol.pdf
28. Stuart JJ, Pisko EJ. Choline magnesium trisalicylate does not impair platelet aggregation. *Pharnatheraoeutica*. 1981; **2**: 547.
29. Foeldvari I, Burgos-Varos R, Thon A, Tuerck D. High response rate in the phase 1/11study of meloxicam in juvenile rheumatoid arthritis. *Journal of Rheumatology*. 2002; **29**: 1079–83.
30. Stempak D, Gammon J, Klein J *et al*. Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clinical Pharmacology and Therapeutics*. 2002; **72**: 490–7.
31. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selectiev COX -2 inhibitors. *Journal of the American Medical Association*. 2001; **286**: 954–9.
32. Williams D, Patel A, Howard R. Pharmacogenetics of codeine metabolism in an urban population of children and its implication for analgesic reliability. *British Journal of Anaesthesia*. 2002; **89**: 839–45.
33. Poyhia R, Seppala T. Lipid solubility and protein binding of oxycodone in vitro. *Pharmacology and Toxicology*. 1994; **74**: 23–7.
34. Pelkonen O, Kaltiala EH, Larmi TKL *et al*. Comparison of activities of drug metabolizing enzymes in human fetal and adult liver. *Clinical Pharmacology and Therapeutics*. 1973; **14**: 840–6.
35. Ross J, Riley J, Welsh K. Genetic variation in the catechol-o-methyl-transferase gene is associated with response to morphine in cancer patients. In: Flor H, Kalso E, Dostrovsky JO (eds). *Proceedings of the 11th World Congress on Pain*. Seattle: IASP Press, 2006: 461–7.
36. McRorie TI, Lynn A, Nespeca MK *et al*. The maturation of morphine clearance and metabolism. *American Journal of Diseases of Children*. 1992; **146**: 972–6.
37. Bhat R, Chari G, Gulati A *et al*. Pharmacokinetics of a single dose of morphine in pre-term infants during the first week of life. *Jounal of Pediatrics*. 1990; **117**: 477–81.
38. Pokela ML, Olkkala KT, Seppala T *et al*. Age-related morphine kinetics in infants. *Developmental Pharmacology and Therapeutics*. 1993; **20**: 26–34.
39. Stanski DR, Greenblatt DJ, Lowenstein E. Kinetics of intravenous and intramuscular morphine. *Clinical Pharmacology and Therapeutics*. 1978; **24**: 52–9.
40. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. *Clinical Pharmacology and Therapeutics*. 1988; **44**: 128–36.
* 41. Cherny NI, Foley KM. Nonopioid and opioid analgesic pharmacotherapy of cancer pain. *Hematology/Oncology Clinics of North America*. 1996; **10**: 79–102.
* 42. Collins JJ, Geake J, Grier HE *et al*. Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. *Jounal of Pediatrics*. 1996; **129**: 722–8.
43. Collins C, Koren G, Crean P *et al*. Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesthesia and Analgesia*. 1985; **64**: 1078–80.
44. Koren G, Goresky G, Crean P *et al*. Unexpected alterations in fentanyl pharmacokinetics in children undergoing cardiac surgery: age related or disease related? *Developmental Pharmacology and Therapeutics*. 1986; **9**: 183–91.
45. Koren G, Goresky G, Crean P *et al*. Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery. *Anesthesia and Analgesia*. 1984; **63**: 577–82.
46. Johnson K, Erickson J, Holley F, Scott J. Fentanyl pharmacokinetics in the pediatric population. *Anesthesiology*. 1984; **61**: A441.
47. Gauntlett IS, Fisher DM, Hertzka RE *et al*. Pharmacokinetics of fentanyl in neonatal humans and lambs: effects of age. *Anesthesiology*. 1988; **69**: 683–7.
* 48. Schechter NL, Weisman SJ, Rosenblum M *et al*. The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics*. 1995; **95**: 335–9.
49. Payne R, Coluzzi P, Hart L *et al*. Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. *Journal of Pain and Symptom Management*. 2001; **22**: 575–83.
50. Collins JJ, Dunkel I, Gupta SK *et al*. Transdermal fentanyl in children with cancer: feasibility, tolerability, and pharmacokinetic correlates. *Journal of Pediatrics*. 1999; **134**: 319–23.
51. Hunt A, Goldman A, Devine T, Phillips M. Transdermal fentanyl for pain relief in a paediatric palliative care population. *Palliative Medicine*. 2001; **15**: 405–12.
52. Tamsen A, Hartvig P, Fagerlund C *et al*. Patient-controlled analgesic therapy, part 1: pharmacokinetics of pethidine in the pre- and postoperative periods. *Clinical Pharmacokinetics*. 1982; **7**: 149–63.
53. Hamunen K, Maunuksela EL, Seppala T *et al*. Pharmacokinetics of iv and rectal pethidine in children undergoing ophthalmic surgery. *British Journal of Anaesthesia*. 1993; **71**: 823–6.

54. Koska AJ, Kramer WG, Romagnoli A *et al*. Pharmacokinetics of high dose meperidine in surgical patients. *Anesthesia and Analgesia*. 1981; **60**: 8–11.
55. Pokela ML, Olkkala KT, Koivisto M *et al*. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. *Clinical Pharmacology and Therapeutics*. 1992; **52**: 342–9.
56. Mather LE, Tucker GT, Pflug AE *et al*. Meperidine kinetics in man: intravenous injection in surgical patients and volunteers. *Clinical Pharmacology and Therapeutics*. 1975; **17**: 21–30.
57. Kaiko RF, Foley KM, Grabinsky PY *et al*. Central nervous system excitatory effects of meperidine in cancer patients. *Annals of Neurology*. 1983; **13**: 180–5.
58. Berde CB, Sethna NF, Holzman RS *et al*. Pharmacokinetics of methadone in children and adolescents in the perioperative period. *Anesthesiology*. 1987; **67**: A519.
* 59. Berde CB, Beyer JE, Bournaki MC *et al*. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *Jounal of Pediatrics*. 1991; **119**: 136–41.
60. Kapelushnik J, Koren G, Solh H *et al*. Evaluating the efficacy of EMLA in alleviating pain associated with lumbar puncture: comparison of open and double-blinded protocols in children. *Pain*. 1990; **42**: 31–4.
* 61. Miser AW, Goh TS, Dose AM *et al*. Trial of a topically administered local anesthetic (EMLA cream) for pain relief during central venous port accesses in children with cancer. *Journal of Pain and Symptom Management*. 1994; **9**: 259–64.
62. Van Kan HJM, Egberts ACG, Rijnvos WPM *et al*. Tetracaine versus lidocaine-prilocaine for preventing venipuncture-induced pain in children. *American Journal of Health-system Pharmacy*. 1997; **54**: 388–92.
* 63. Houck CS, Sethna NF. Transdermal analgesia with local anesthetics in children: review, update and future directions. *Expert Review of Neurotherapeutics*. 2005; **5**: 625–34.
64. Bruera E, Brenneis C, Michaud M *et al*. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. *Cancer*. 1988; **62**: 407–11.
65. Gourlay G, Boas RA. Fatal outcome with use of rectal morphine for postoperative pain control in an infant. *British Medical Journal*. 1992; **304**: 766–7.
* 66. Mackie AM, Coda BC, Hill HF. Adolescents use patient controlled analgesia effectively for relief for relief from prolonged oropharyngeal mucositis pain. *Pain*. 1991; **46**: 265–9.
67. Dunbar PJ, Buckley P, Gavrin JR *et al*. Use of patient-controlled analgesia for pain control for children receiving bone marrow transplants. *Journal of Pain and Symptom Management*. 1995; **10**: 604–11.
* 68. Galer BS, Coyle N, Pasternak GW *et al*. Individual variability in the response to different opioids: report of five cases. *Pain*. 1992; **49**: 87–91.
69. Portenoy RK. Opioid tolerance and responsiveness: research findings and clinical observations. In: Gebhart GF, Hammond DI, Jensen TS (eds). *Progress in pain research and management*. Seattle: IASP Press, 1994: 615–19.
* 70. Inturrisi CE, Portenoy RK, Max M *et al*. Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain. *Clinical Pharmacology and Therapeutics*. 1990; **47**: 565–77.
* 71. Drake R, Longworth J, Collins JJ. Opioid rotation in children with cancer. *Journal of Palliative Medicine*. 2004; **7**: 419–22.
* 72. Lussier D, Portenoy RK. Adjuvant analgesics in pain management. In: Doyle D, Hanks GWC, Cherny N, Calman K (eds). *Oxford textbook of palliative medicine*. Oxford: Oxford University Press, 2004: 349–78.
73. Watson C, Evans R, Reed K *et al*. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology*. 1982; **32**: 671–3.
* 74. Max MB. Antidepressants as analgesics. In: Fields HL, Liebeskind JC (eds). *Progress in pain research and pain management*. Seattle: IASP Press, 1994: 229–46.
75. Diamond S, Baltes B. Chronic tension headache treatment with amitriptyline – a double blind study. *Headache*. 1971; **11**: 110–16.
76. Couch J, Ziegler D, Hassanein R. Amitriptyline in the prophylaxis of migraine: effectiveness and relationship of antimigraine and antidepressant effects. *Neurology*. 1976; **26**: 121–7.
77. Frank R, Kashani J, Parker J *et al*. Antidepressant analgesia in rheumatoid arthritis. *Journal of Rheumatology*. 1988; **15**: 1632–8.
78. Ward NG. Tricyclic antidepressants for chronic low back pain: mechanisms of action and predictors of response. *Spine*. 1986; **11**: 661–5.
* 79. Magni G. The use of antidepressants in the treatment of chronic pain. *Drugs*. 1991; **42**: 730–48.
* 80. McQuay HJ, Tramer M, Nye BA *et al*. A systematic review of antidepressants in neuropathic pain. *Pain*. 1996; **68**: 217–27.
81. Heiligenstein E, Gerrity S. Psychotropics as adjuvant analgesics. In: Schechter NL, Berde CB, Yaster M (eds). *Pain in infants, children, and adolescents*. Baltimore: Williams & Wilkins, 1993: 173–7.
82. Biederman J, Baldessarini RJ, Wright V *et al*. A double-blind placebo controlled study of desipramine in the treatment of ADD: II. Serum drug levels and cardiovascular findings. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1989; **28**: 903–11.
83. Forrest WH, Brown BW, Brown CR *et al*. Dextroamphetamine with morphine for the treatment of postoperative pain. *New England Journal of Medicine*. 1977; **296**: 712–15.
84. Bruera E, Miller MJ, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. *Pain*. 1992; **48**: 163–6.
85. Bruera E, Faisinger R, MacEachern T, Hanson J. The use of methylphenidate in pateints with incident pain receiving regular opiates: a preliminary report. *Pain*. 1992; **50**: 75–7.

86. Yee JD, Berde CB. Dextroamphetamine or methylphenidate as adjuvants to opioid analgesia for adolescents with cancer. *Journal of Pain and Symptom Managment*. 1994; **9**: 122–5.
87. Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. *Journal of Pain and Symptom Managment*. 1994; **9**: 442–5.
88. Tannock I, Gospodarowicz M, Meakin W *et al*. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *Journal of Clinical Oncology*. 1989; **7**: 590–7.
89. Weinstein JD, Toy FJ, Jaffe ME, Goldberg HI. The effect of dexamethasone on brain edema in patients with metastatic brain tumors. *Neurology*. 1973; **23**: 121–9.
90. Greenberg HS, Kim J, Posner JB. Epidural spinal cord compression from metastatic tumor: results with a new treatment protocol. *Annals of Neurology*. 1980; **8**: 361–6.
91. Khurana DS, Riviello J, Helmers S *et al*. Efficacy of gabapentin therapy in children with refractory partial seizures. *Jounal of Pediatrics*. 1996; **128**: 829–33.
92. Silberstein EB, Williams C. Strontium-89 therapy for painful osseous metastases. *Journal of Nuclear Medicine*. 1985; **26**: 345–8.
93. Westlin JE, Letocha H, Jakobson S *et al*. Rapid, reproducible pain relief with [131I]iodine-meta-iodobenzylguanidine in a boy with disseminated neuroblastoma. *Pain*. 1995; **60**: 111–14.
94. Beaver WT, Wallenstein S, Houde RW, Rogers A. A comparison of the analgesic effects of methotrimeprazine and morphine in patients with cancer. *Clinical Pharmacology and Therapeutics*. 1966; **7**: 436–46.
95. Collins JJ, Grier HE, Sethna NF, Berde CB. Regional anesthesia for pain associated with terminal malignancy. *Pain*. 1996; **65**: 63–9.
96. Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. *Journal of Palliative Care*. 1994; **10**: 31–8.
97. Wang Y, Mitchell J, Moriyama K *et al*. Age-dependent morphine tolerance development in the rat. *Anesthesia and Analgesia*. 2005; **100**: 1733–9.
98. Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP. Age-dependent opioid escalation in chronic pain patients. *Anesthesia and Analgesia*. 2005; **100**: 1740–5.
99. Porter J, Jick H. Addiction is rare in patients treated with narcotics. *New England Journal of Medicine*. 1980; **302**: 123.