



Original Release date: September, 2007 Updated: February, 2010 Expiration Date: March, 2012

The pediatric population is at risk of inadequate pain management, with age-related factors affecting pain management in children. Children are often given minimal or no analgesia for procedures that would routinely be treated aggressively in adults. Although much is now known about pain management in children, it has not been widely or effectively translated into routine clinical practice.

Educational Objectives

- Describe developmentally appropriate strategies and tools for assessing pain in children.
- Utilize pharmacologic and nonpharmacologic treatments for pain in children.

Copyright © 2010 American Medical Association. All rights reserved. The contents of this CME program may not be reproduced in any form without written permission from the AMA. This CME program does not define a standard of care, nor is it intended to dictate an exclusive course of management. Standards of medical care are determined on the basis of all the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve.

The products appearing in this continuing medical education program are given for information purposes only. Their inclusion does not imply AMA endorsement, nor does omission of any product indicate AMA disapproval.

The American Medical Association designates this education activity for a maximum of 1 AMA PRA Category 1 Credit™. Physician should only claim credit commensurate with the extent of their participation in the activity.

This continuing medical education program is intended for primary care physicians and those physicians who care for patients experiencing pain.

Financial Support

This CME module is supported through an unrestricted educational grant from Purdue Pharma L.P. and produced in accordance with the AMA Standards for Industry-Supported Multimedia Continuing Medical Education and Other Communications.

Contact Information

Inquire about the content of this CME Program or Technical Issues
R. Mark Evans, PhD
American Medical Association
515 North State Street
Chicago, IL 60654
mark.evans@ama-assn.org

Instructions for CME Credit

To obtain your *AMA PRA Category 1 Credit™* for this module you will need to review the CME Information front matter, read the module content and then register and complete the self-assessment and program evaluation questions online. These can be found at the end of each online module. You will be able to print your CME certificate. Follow these steps to obtain your CME credit and certificate:

1. Complete the self-assessment and the program evaluation questions and then click the "submit button".
2. The CME certificate will then appear and can be printed out. All data from the online forms will be automatically reported to the AMA. Your name will be stored in the AMA CME database for future transcript requests. You need do nothing further once you have completed the forms and printed your certificate.

Repeat these steps for each module to obtain your certificate. If you have any questions, please contact: mark.evans@ama-assn.org.

Hardware and Software Requirements

For this CME program your computer should be Windows 98 or higher compatible. Internet Explorer 6.0 or Netscape 4.7 (or higher) and Macromedia Flash 6.0 (or higher) are also required. If you are using a modem to connect to the Internet, you will need a modem speed of at least 56K. Macromedia's Flash Player is required to complete the self-assessment and print your certificate, and it is available free at www.macromedia.com. *As you will be printing your CME certificate online, your computer must be connected to a printer.*



CME Principal Faculty

American Medical Association

Perry G. Fine, MD, Content Consultant
Associate Medical Director
Pain Management Center
Professor of Anesthesiology
University of Utah
Salt Lake City, UT

Pauline Lesage, MD, LLM, Contributing Author
Medical Director, Jacob Perlow Hospice
Beth Israel Medical Center
Associate Professor, Family Medicine
Albert Einstein School of Medicine
New York, NY

Philipp M. Lippe, MD, Content Reviewer
Executive Medical Director
American Academy of Pain Medicine
Clinical Professor of Neurosurgery
Stanford University
Stanford, CA

Arthur G. Lipman, PharmD, Content Consultant
Professor, College of Pharmacy & Director
of Clinical Pharmacology
Pain Management Center, Pain Medicine
and Palliative Care Advisory Group
Huntsman Cancer Institute
University of Utah Health Sciences Center
Salt Lake City, UT

Russell K. Portenoy, MD, Contributing Author,
Planning Committee
Chairman, Department of Pain Medicine
and Palliative Care
Beth Israel Medical Center
New York, NY
Professor of Neurology and Anesthesiology
Albert Einstein College of Medicine
Bronx, NY

American Academy of Neurology

Charles E. Argoff, MD, Content Consultant
Co-Director, Cohn Pain Management Center
Assistant Professor of Neurology
North Shore University Hospital
Manhasset, NY

American College of Obstetricians and Gynecologists

Jonathan S. Berek, MD, Content Reviewer
Professor and Chair, College of Applied Anatomy
Executive Vice Chair, Department of OB/GYN
Chief, Gynecology Service
Chief, Division of Gynecologic Oncology
David Geffen School of Medicine at UCLA
Los Angeles, CA

American Society of Anesthesiologists

May L. Chin, MD, Content Reviewer
Professor of Anesthesiology
Director, Pain Management Center
George Washington University Hospital
Washington, DC

American Pain Society

Scott M. Fishman, MD, Content Reviewer
Professor and Chief, Division of Pain Medicine
Department of Anesthesiology and Pain Medicine
University of California , Davis
Sacramento, CA

American Academy of Pain Medicine

Kenneth A. Follert, MD, PhD, Content Reviewer
Professor, Neurosurgery
University of Iowa Hospital & Clinics
Iowa City, IA

American Academy of Pediatrics

Constance S. Houck, MD, Contributing Author
Senior Associate in Anesthesia, Department
of Anesthesiology, Perioperative and Pain Medicine
Children's Hospital
Assistant Professor, Anesthesia
Harvard Medical School
Boston, MA

American Academy of Orthopaedic Surgeons

L. Andrew Koman , MD, Content Consultant
Vice Chair and Professor, Department
of Orthopedic Surgery
Wake Forest University School of Medicine
Winston-Salem, NC

American Academy of Physician Assistants

Sharon Kulesz, PA-C, Content Reviewer
Assistant Director of Professional Affairs, AAPA
Alexandria, VA

American Academy of Family Physicians

Cheryl L. Lambing, MD, Content Reviewer
Assistant Clinical Professor
University of California , Los Angeles
Ventura, CA

American Society of Addiction Medicine

Seddon R. Savage, MD, MS, Content Consultant
Pain Consultant, Manchester VAMC
Associate Professor of Anesthesiology
Adjunct Faculty, Dartmouth Medical School
Bradford, NH

American Psychiatric Association

Jon Strelzer, MD, Content Consultant
Professor, Department of Psychiatry
John A. Burns School of Medicine
University of Hawaii at Manoa
Honolulu, HI

American College of Emergency Physicians

Knox H. Todd, MD, MPH , FACEP, Content Consultant
Director, Pain and Emergency Medicine Initiative
Adjunct Associate Professor, Rollins School
of Public Health
Emory University School of Medicine
Atlanta, GA

Planning Committee

R Barry Dickinson, PhD, CME Program Committee
American Medical Association

Mark Evans, PhD
American Medical Association

Patti Fitzgerald
American Medical Association

Russell K. Portenoy, MD, Contributing Author,
Planning Committee
Chairman, Department of Pain Medicine
and Palliative Care
Beth Israel Medical Center
New York, NY
Professor of Neurology and Anesthesiology
Albert Einstein College of Medicine
Bronx, NY

Art and Illustration

Copyright © 2007-2010 Scott Bodell
Bodell Communications, Inc.



Disclosure Policy

It is the policy of the AMA to ensure balance, independence, objectivity, and scientific rigor in all of its activities. This AMA CME program has been independently planned by the AMA and complies with the AMA Division of Healthcare Education Products and Standards' Policies and Procedures for Resolving Conflicts of Interest (COI) for their CME activities, to identify and resolve COI, review faculty and staff disclosure statements, and determine the level of participation of the planning committee members, and principal faculty. Faculty and planning committee members have attested that their financial relationships do not affect their ability to present well-balanced evidence-based content for this activity.

In order to assure the highest quality of certified CME programming, and to comply with the ACCME Standards for Commercial Support, the AMA requires that all faculty, planning committee and AMA CME Program Committee members disclose relevant financial relationships with any commercial or proprietary entity producing health care goods or services relevant to the content being planned or presented. The following disclosures are provided:

CME Advisory Board

- Dr. Argoff: Consultant: Pricara, Pfizer, Lilly, Forest, Bristol Myers Squibb, King Pharmaceuticals, sanofi-aventis;
Grant support: Endo;
Speaker's Bureau: Endo, Pricara, Pfizer, Lilly, Forest, King Pharmaceuticals
- Dr. Berek: Nothing relevant to disclose
- Dr. Chin: Nothing relevant to disclose
- Dr. Ferrell: Nothing relevant to disclose
- Dr. Fine: Advisory Board: Endo, Cephalon, Lilly, Alpharma, Wyeth & GlaxoSmithKline
- Dr. Fishman: Nothing relevant to disclose
- Dr. Follett: Nothing relevant to disclose
- Dr. Houck: Nothing relevant to disclose
- Dr. Koman: Consultant, Wright Medical; Medical Director/Board member, DT Scimed, Kerannetics
- Dr. Kulesz: Nothing relevant to disclose
- Dr. Lambing: Nothing relevant to disclose
- Dr. Lesage: Nothing relevant to disclose
- Mr. Lipman: Consultant: Pfizer, Progenics, Johnson & Johnson, Biovail, NiCox;
Speaker's Bureau: Johnson & Johnson, Forest/Cypress
- Dr. Lippe: Nothing relevant to disclose
- Dr. Portenoy: Consultant: Alpharma, Ameritox, Cephalon, GW Pharma, Grupo Ferrer, Insys Therapeutics, King Pharmaceuticals, Neuromed, Purdue Pharma, Shire Pharmaceuticals, Titan, Transcept Pharmaceuticals, WEX Pharmaceuticals, Wyeth, Xenon
Grants: Archimedes Pharmaceuticals, Cephalon, Endo Pharmaceuticals, Fralex, GW Pharmaceuticals, King Pharmaceuticals, Pfizer, Inc., Purdue Pharma, United BioSource Corp., Wyeth
- Dr. Savage: Advisory Board: Ameritox, Registrat, Meda
- Dr. Todd: Consultant: Purdue Pharma; Research Grant, Baxter

AMA Editorial Staff

- Dr. Evans: Nothing relevant to disclose
- Dr. Dickinson: Nothing relevant to disclose
- Ms. Fitzgerald: Nothing relevant to disclose
- Dr. Portenoy: Consultant: Alpharma, Ameritox, Cephalon, GW Pharma, Grupo Ferrer, Insys Therapeutics, King Pharmaceuticals, Neuromed, Purdue Pharma, Shire Pharmaceuticals, Titan, Transcept Pharmaceuticals, WEX Pharmaceuticals, Wyeth, Xenon
Grants: Archimedes Pharmaceuticals, Cephalon, Endo Pharmaceuticals, Fralex, GW Pharmaceuticals, King Pharmaceuticals, Pfizer, Inc., Purdue Pharma, United BioSource Corp., Wyeth

Disclosure of Off-Label Uses

The content of this CME publication may contain discussion of off-label uses of some of the agents mentioned. Please consult the product prescribing information for full disclosure of labeled uses.

CME Needs Assessment

Pain is one of the most common reasons for patients to seek medical attention and one of the most prevalent medical complaints in the US.¹⁻³ According to the 2006 National Center for Health Statistics Report, one in 10 Americans overall and three in five of those 65 years or older said that they experienced pain that lasted a year or more.² More than one-quarter of adults said they had experienced low back pain, and 15% of adults experienced migraine or severe headache in the past three months. Between the periods 1988-94 and 1999-2002, the percentage of adults who took a narcotic drug to alleviate pain in the past month rose from 3.2 percent to 4.2 percent.

For the millions of Americans who experience persistent pain, the impact on function and quality of life can be profound.²⁻⁴ Pain is associated with high utilization of health care⁴ and the societal costs related to treatment are compounded by the loss in productivity associated with persistent pain. Lost productive time from common pain conditions among workers costs an estimated \$61.2 billion per year and most of this is related to reduced performance while at work.⁵ The total annual cost of poorly controlled persistent pain most likely exceeds \$100 billion.

Physicians and other healthcare professionals need current, state-of-the-art education to assist them in developing the skills required to evaluate and manage pain in children. This CME program reviews important considerations in pain management in children. Strategies for assessing pain, specific pain assessment tools, and pharmacologic and nonpharmacologic management options specific to children are also addressed.

1. Watkins EA, Wollan PC, Melton LJ 3rd, Yawn BP. A population in pain: report from the Olmsted County health study. *Pain Med.* 2008;9(2):166-74.

2. <http://www.cdc.gov/nchs/hus.htm>

3. Blay SL, Andreoli SB, Gastal FL. Chronic painful physical conditions, disturbed sleep and psychiatric morbidity: results from an elderly survey. *Ann Clin Psychiatry.* 2007 Jul-Sep;19(3):169-74.

4. Von Korff M, Lin EH, Fenton JJ, Saunders K. Frequency and priority of pain patients' health care use. *Clin J Pain.* 2007 Jun;23(5):400-8.

5. Stewart, WF, Ricci, JA, Chee, E, Morganstein D, & Lipton R. (2003). Lost productive time and cost due to common pain conditions in the US workforce. *JAMA.* 2003; 290(18):2443-2454.



Introduction

It is now well accepted by neuroscientists and pain specialists that the nervous system is sufficiently developed to process nociception before birth, and consequently, children must be assumed to experience pain from birth onward.¹ Indeed, due to a more robust inflammatory response and the lack of a central inhibitory influence, infants and young children actually may experience a greater neural response, *i.e.*, more pain sensation and pain-related distress, following a noxious stimulus than do adults. The impact of painful experience on the young nervous system is so significant that long-term effects can occur, including a lowered pain tolerance for months after a pain-producing event.² Given the certainty that neonates and preverbal children experience pain, the long history of undertreatment^{3,4} cannot be justified by the lack of easy communication with these patients, and certainly not with older children and adolescents. The multifactorial sources of undertreatment of pediatric pain should be understood and provide the basis for professional and parental education, and system changes, that are necessary to yield best practices in pediatric pain control.

Misconceptions That Can Lead to Undertreatment of Pain in Children
The American Academy of Pediatrics and the American Pain Society have issued a joint statement recommending that pain be recognized and treated more aggressively in children. They point to several misconceptions that can lead to undertreatment of pain in children:⁵

- The myth that infants and children do not feel pain, or suffer less from it than adults.
- Lack of routine pain assessment in children.

- Lack of knowledge regarding newer modalities and proper dosing strategies for the use of analgesics in children.
- Fears of respiratory depression or other adverse effects of analgesic medications.
- The belief that preventing pain in children takes too much time and effort.

Pain Assessment in Infants and Children

Because children have a limited range of experience and may be unable to use words that adequately express their discomfort, determining just how much pain a child is experiencing can be difficult. Cognitive, behavioral, emotional, and psychosocial factors (*e.g.*, family learning, culture), and other factors (*e.g.*, gender) play a role in a child's pain experiences, with children and adolescents responding to noxious experiences differently at different developmental stages. Observational pain scales have been validated for neonates and infants to allow pain assessment in those unable to verbalize their pain. These scales, though essential, also respond to distress from causes other than pain, such as hunger, fear or anxiety (*e.g.*, from parental separation). Simple self-report scales using facial expressions or small objects to describe pieces of hurt (*i.e.*, Poker Chip Tool) have been devised to allow preschool and school age children to more accurately describe the intensity of their pain.

Observational Pain Scales for Neonates and Infants

With the widespread use of screening blood tests in the newborn and the large number of neonatal circumcisions performed in hospitals throughout the U.S., researchers have been developing assessment tools and studying the effects of pain in newborns

FLACC Behavioral Pain Assessment

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractable	Difficulty to console or comfort

Each of the five categories is scored from 0-2, resulting in a total score between 0 and 10. The FLACC scale was developed by Sandra Merkel, MS, RN, Terri Voepel-Lewis, MS, RN, and Shobha Malviya, MD, at C. S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI. Copyright © 2002, The Regents of the University of Michigan. Reproduced with permission.



for a number of years.⁷ These pain assessment scales have been validated in studies of preterm and term neonates and have aided in the development of similar observational scales for toddlers and cognitively impaired children. Most combine easily obtained physiologic parameters such as heart rate and oxygen saturation with facial expressions such as brow bulge, eye squeeze, and nasolabial furrow and body movements to determine the degree of discomfort. The most commonly used scales in newborns are the Premature Infant Pain Profile (PIPP) and the CRIES Postoperative Pain Scales.⁶⁻⁸ The FLACC (Face, Legs, Activity, Cry and Consolability) Scale is a behavioral scale that has been validated for assessment of postoperative pain in children between the ages of 2 months and 7 years.⁹ After observing a child for one to five minutes, a pain score is obtained by reviewing the descriptions of behavior and selecting the number that most closely matches the observed behavior.

Self-Report Scales for Children

Starting at about 18 months of age, children have acquired words for pain, and 3- or 4-year-old children may be able to report pain, indicate its location, and describe its characteristics. If self-report is possible, it is the preferred strategy for information-gathering about pain. Progress has been made in creating and validating self-report scales and in understanding the developmental and socioenvironmental influences on pain report, but research in this area is needed.¹⁰ Self-report pain scales developed for young children include the Poker Chip Scale, Wong-Baker Faces Scale and the Oucher Scale.¹¹⁻¹³ The Oucher Scale (www.oucher.org) which is available in different ethnic versions, permits children to rate their pain intensity by matching it to photographs of other children's faces depicting increasing levels of pain. The Poker Chip Scale asks children to quantify their pain in "pieces of hurt," with more poker chips representing more pain. Body outlines allow young children to point to the location of their pain. As school age children learn the proportionality of numbers and colors, they can generally use the same scales as adults (*i.e.*, Visual Analog Scale, Numeric Rating Scale) without difficulty.

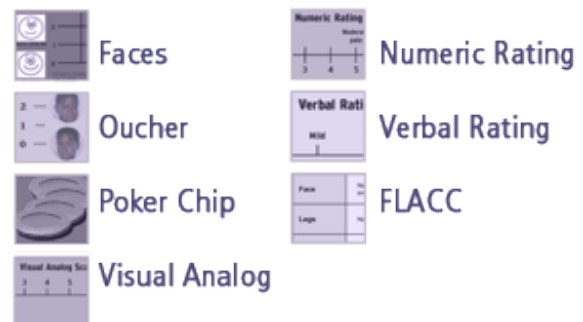
Interpreting pain scales can be difficult in young children since their ratings are based on prior experiences of pain. Thus, when young children use the upper end of a scale to rate their pain, they are indicating its severity relative to their prior pain experience.¹⁴ For young children, an injury or procedure might be the strongest pain they have experienced whereas older children and adults may rate the same injury as less painful, because they have experienced a more diverse array of pain.

Several questionnaires have been developed for children with chronic or persistent pain. These include, among others, the Varni-Thompson Pediatric Pain Questionnaire, and the Children's Comprehensive Pain Questionnaire.^{15,16}

Poker Chip Tool Instruction Sheet

- Say to the child: "I want to talk with you about the hurt you may be having right now."
- Align the chips horizontally in front of the child on the bedside table, a clipboard, or other firm surface.
- Tell the child, "These are pieces of hurt." Beginning at the chip nearest the child's left side and ending at the one nearest the right side, point to the chips and say, "This (first chip) is a little bit of hurt and this (fourth chip) is the most hurt you could ever have."
- For a young child or for any child who may not fully comprehend the instructions, clarify by saying, "That means this (one) is just a little hurt, this (two) is a little more hurt, this (three) is more yet, and this (four) is the most hurt you could ever have."
- Do not give children an option for zero hurt. Research with the Poker Chip Tool has verified that children without pain will so indicate by responses such as, "I don't have any."
- Ask the child, "How many pieces of hurt do you have right now?"
- After initial use of the Poker Chip Tool, some children internalize the concept "pieces of hurt." If a child gives a response such as "I have one right now." before you ask or before you lay out the poker chips, proceed with asking how many pieces of hurt the child has now.
- Record the number of chips on a pain flow sheet.
- Clarify the child's answer by words such as, "Oh, you have a little hurt? Tell me about the hurt."

Source: Hester NO, Foster R, Kristensen K. Measurement of pain in children: generalizability and validity of the Pain Ladder and the Poker Chip Tool. In: Tyler DC, Krane EJ, eds. Pediatric pain. Vol. 51. *Advances in Pain Research and Therapy*. New York: Raven Press, Ltd.; 1990. p. 79-84.





Management of Acute Pain in Children

Acute pain is far more common than chronic pain in children. Pain from injury or illness typically is transitory; most can be easily managed by the patient and caretakers. Iatrogenic acute pain also is common and extends from the increasing number of needle stick procedures (immunizations, screening blood tests) that are performed as a part of preventive medicine strategies to acute severe pain related to surgery or other procedures done to address a serious medical problem. Unrelieved pain can lead to considerable anxiety and distress and, in some instances, can have long-term physiological and behavioral consequences. Though it is impossible to prevent all sources of pain, information is now available to aid practitioners in providing safe and effective analgesic modalities for both prevention and treatment of childhood pain.

Nonpharmacologic Pain Management

Nonpharmacologic approaches for the treatment of pain in children include psychological strategies, education and parental support. For children undergoing repeated painful procedures, cognitive-behavioral therapy interventions, which decrease anxiety and distress, can be quite effective.¹⁷ The aim of such therapies is to provide responses that may help children master a distressing situation, ideally in a manner consistent with their basic coping strategies. Most of these techniques take time to learn and master, so simple distraction techniques that divert attention away from painful stimuli, or positive incentive techniques which provide a small reward (e.g., stickers or prizes) for attempts at mastery of their responses, can be effective for children undergoing occasional procedures. These techniques are designed to decrease anxiety, but are not adequate as the sole means of pain relief for most painful procedures.

Special Considerations in Treating Infants and Children

When treating pain in infants it is important to understand that although most of the major organ systems are anatomically well developed at birth, their functional maturity is often delayed. In the first months of life in both preterm and full-term newborns, these systems rapidly mature, most approaching a functional level similar to adults before 3 months of age. General principles of newborn physiology and its effects on the pharmacology of opioids and local anesthetics are described in the following text:

- Most analgesics (including opioids and local anesthetics) are conjugated in the liver. Newborns, and especially premature infants have delayed maturation of the enzyme systems involved in drug conjugation, including sulfation, glucuronidation, and oxidation. Several of these

hepatic enzyme systems, including cytochrome P450 subtypes, and the mixed-function oxidases, mature at varying rates over the first 1 to 6 months of life.¹⁸

- Glomerular filtration rates are diminished in the first week of life, especially in premature infants, but generally are sufficiently mature to clear medications and metabolites by 2 weeks of age.¹⁹
- Newborns have a higher percentage of body weight as water and less as fat compared with older patients. Water soluble drugs, therefore, often have larger volumes of distribution.
- Newborns have reduced plasma concentrations of both albumin and alpha-1 acid glycoprotein than older children and adults. For some drugs, this may lead to higher concentrations of unbound drug (active), and thereby greater drug effect or drug toxicity.
- Newborns, and especially premature infants, have diminished ventilatory responses to hypoxemia and hypercarbia.^{20,21} These ventilatory responses can be further impaired by CNS depressant drugs such as opioids and benzodiazepines.

Acetaminophen

Due to its excellent safety profile and lack of significant side effects, acetaminophen is the most commonly used analgesic agent in pediatric practice. It is a mainstay for mild to moderate pain, and is often combined with opioid analgesics for patients with more severe pain (*i.e.*, acetaminophen with codeine).

Toxicity can result when the toxic metabolite of acetaminophen, acetyl-p-benzoquinone-imine (NAPQI), is produced in such high quantities that there is not enough glutathione peroxidase (GSH) to bind to it. Infants and children produce high levels of GSH as a part of hepatic growth and this may provide some protection against the hepatotoxicity produced by overdose. This was suggested in a rodent study that compared weanling to adult rats.²²

Acetaminophen is available orally in several tablet and liquid formulations. Oral dosing of 10 to 15 mg/kg is commonly recommended, though single oral doses of 20 mg/kg appear quite safe in children. Neonates have a slower elimination half-life so the drug must be given less frequently. Daily maximum oral dosing is recommended not to exceed 90 mg/kg for children, 60 mg/kg for term neonates <10 days of age, and 45 mg/kg for premature infants >34 weeks gestational age.²³



Rectal preparations of acetaminophen are available for infants and toddlers who are unable or unwilling to take this medication orally. A series of studies has confirmed that rectal absorption is slow, somewhat variable, and comparatively inefficient. Single rectal doses of 30 to 45 mg/kg produced plasma concentrations that were generally in the effective range, and never in a range associated with hepatotoxicity.^{24,25} Following these large rectal doses, there is a comparatively slow decline in plasma concentrations. Based on a 24-hour kinetic study, it was recommended that initial doses of 35 to 40 mg/kg be followed by subsequent doses of 20 mg/kg, with the dosing interval extended to at least 6 hours.²⁵ If a large rectal dose is to be followed by oral dosing, it is also recommended that a first oral dose be given no sooner than 6 hours after the initial dose. Dosage guidelines for acetaminophen and the most commonly used NSAIDs in children can be found in the table.

Nonsteroidal Anti-inflammatory Drugs

Except in the newborn period, when the half-life after administration is significantly longer, the pharmacodynamics and pharmacokinetics of NSAIDs in children are not much different than in adults.²⁶ Although the potential for GI, renal and other toxicities exist, the incidence of these problems in young and older children may be less than that encountered during treatment of adults,²⁷ perhaps due to the uncommon occurrence of the comorbidities and polypharmacy that predispose to problems.

Ibuprofen is frequently chosen for mild to moderate pain, because it is available in a liquid form allowing for easy administration to younger children. Since it became available as an over-the-counter medication for fever reduction as well as pain relief, there is a large amount of clinical experience in infants and children with this drug. A review of short-term ibuprofen use in a large cohort of children revealed no increase in clinically significant renal or GI side effects compared to acetaminophen.²⁸

Ketorolac is the only parenteral NSAID currently available in the U.S. It has been used both as an adjuvant to opioid analgesia, and as a single agent for the treatment of postoperative pain in children and adolescents. One study demonstrated that the administration of a single dose of 0.8 mg/kg of ketorolac could reduce the need for self-administered opioid analgesia by approximately 30% in the first 12 hours after surgery.²⁹ This led to a significant reduction in urinary retention compared to opioid analgesia alone. Dosage recommendations have been reduced in the last few years to 0.25 to 0.5 mg/kg every 6 hours with no requirement for a loading dose. A review of the short-term use (48 hours) of intravenous ketorolac in over 1,700 children demonstrated a low rate of complications.³⁰

Adult studies have found that, in comparison with traditional NSAIDs, COX-2 inhibitors demonstrate a significantly lower incidence of gastritis or ulcers, and preservation of platelet function. Only the COX-2 inhibitor, celecoxib, is available for oral administration. There have been no pediatric clinical trials of this drug.

Table: Initial Dosage Guidelines for Nonopioid Analgesics*

Drug	Dose (mg/kg)(<60 kg)	Dose (mg)(≥ 60 kg)	Interval (hours)	Daily Maximum Dose (mg/kg)(<60 kg)	Daily Maximum Dose (mg)(≥ 60 k)
Acetaminophen	10-15	650-1000	4	90*	4000
Oral	20†	1000	6	120	
Rectal					
Ibuprofen	5-10	400-600‡	6	40	2400‡
Naproxen	5-6	250-375‡	12	24	1000‡
Aspirin §	10-15	650-1000‡	4	80	3600‡
Ketorolac (IV)	0.25-0.5	15-30	6	2	120

*Maximum daily doses for acetaminophen in term neonates and infants, should be reduced to 60 mg/kg, and to 45 mg/kg in preterm neonates.

†A loading dose of 35-40 mg/kg is recommended when acetaminophen is administered rectally

‡Higher doses may be used in selected cases for treatment of rheumatologic conditions in children.

§Aspirin carries a risk of provoking Reye's syndrome in infants and children. If other analgesics are available, aspirin use should be restricted to indications where anti-platelet or anti-inflammatory effect is required, rather than as a routine analgesic or antipyretic in neonates, infants, or children. Dosing guidelines for aspirin in neonates have not been established.

Reproduced with permission from Berde CB, Sethna NP. Analgesics for the treatment of pain in children. *N Engl J Med.* 2002;347:1094-1103.



Opioid Analgesics

For the vast majority of children, opioids provide excellent analgesia with a wide margin of safety. Developmental differences, however, can make dosing difficult, especially in the first several months of life. In the first week of a newborn's life, the elimination half-life of morphine is more than twice as long as that in older children and adults, as a result of delayed clearance.³¹ This appears to be due to several factors, most important of which is the immaturity of the newborn infant's hepatic enzyme systems. Clearance of morphine is dependent on conjugation of the drug to the metabolites' morphine-3-glucuronide and the morphine-6-glucuronide; the latter contributes a substantial fraction of morphine's analgesic

effects. This reaction is catalyzed by mixed function oxidases and the cytochrome P450 system, which, though present, have attained only a portion of their full function. Fentanyl and sufentanil also have diminished hepatic metabolism in premature and term neonates. Glomerular filtration is reduced in the first week of life, leading to slower elimination of morphine's active metabolites.

These pharmacokinetic differences between neonates and older children must be understood to adjust dosing appropriately and avoid toxicity. Equally important in determining safe opioid dosing in infants is an understanding of the immaturity of central respiratory control mechanisms. Infants in the first 3 to 6 months of life have inadequate and sometime paradoxical ventilatory responses to

Table: Initial Dosage Guidelines for Opioid Analgesics*

Drug	Equianalgesic Doses		Usual Starting IV 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	N/R	N/R	1:2	0.5-1 mg/kg q 3-4 hrs	30-60 mg q 3-4 hr
Morphine	10 mg	30 mg (long-term)	Bolus: 0.1 mg/kg q 2-4 hr Infusion: 0.02 -0.03 mg/kg/hr	Bolus: 5-8 mg q 2-4 hr Infusion: 1.5 mg/hr	1:3	Immediate Release: 0.3 mg/kg q 3-4 hr	Immediate Release: 15-20 mg q 3-4 hr Sustained Release: 30-45 mg q 8-12 hr
Oxycodone	N/A	15-20 mg	N/A	N/A	N/A	0.1-0.2 mg/kg q 3-4 hr	5-10 mg q 3-4 hr
Methadone	10 mg	10-20 mg	0.1 mg/kg †	5-8 mg q 4-8 hr	1:2	0.1 mg/kg q 4-8 hr	10 mg q 4-8 hr
Fentanyl	100 mcg (0.1 mg)	N/A	Bolus: 0.5-1.0 mcg/kg q 1-2 hr Infusion: 0.5-2.0 mcg/kg/hr	Bolus: 25-50 mcg q 1-2 hrs Infusion: 25-100 mcg/hr	N/A	N/A	N/A
Hydromorphone	1.5-2 mg	6-8 mg	Bolus: 0.02 mg q 2-4 hr Infusion: 0.006 mg/kg/hr	Bolus: 1 mg q 2-4 hrs Infusion: 0.3 mg/hr	1.4	0.04-0.08 mg/kg q 3-4 hr	2-4 mg q 3-4 hr
Meperidine+ (pethidine)	75-100 mg	300 mg	Bolus: 0.8-1.0 mg/kg q 2-3 hr	Bolus: 50-75 mg q 2-3 hr	1.4	2-3 mg/kg q 3-4 hr	100-150 mg q 3-4 hr

Doses are for patients over six months of age. All doses are approximate and should be adjusted according to clinical circumstances.

†See text for information about methadone sliding scale administration.

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

Reproduced with permission from Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Eng J Med.* 2002;347:1094-1103.



both hypoxia and hypercapnia.²¹ As a result, they may develop apnea or periodic breathing after receiving even small doses of opioids. Cardiorespiratory monitoring and careful observation is recommended whenever opioids are administered to infants less than 2 to 3 months of age. Premature infants and former premature infants with chronic lung disease continue to show depressed hypoxic drive for several months, and often require careful monitoring after opioid administration up to 5 to 6 months of age.

Oral opioids

Codeine is available in an elixir form and is, therefore, the most commonly administered oral opioid in young children. It is often given in combination with acetaminophen but a safe dosage for children under 3 has not been established. The combination product is not a Schedule II drug in the U.S, which means that it can be prescribed over the phone—a convenient scenario for some physicians. The commercially available acetaminophen/ codeine elixir contains the two drugs in a 10:1 ratio (acetaminophen 120 mg with codeine 12 mg in each 5 ml). When given separately, these two drugs are generally given in a 20:1 to 30:1 ratio (*i.e.*, 10 to 15 mg/kg acetaminophen and 0.5 mg/kg codeine). Therefore, additional acetaminophen is often prescribed to improve analgesia.

Codeine’s analgesic effects derive from its metabolic conversion to morphine. A significant fraction of the general population (ranging from 3% to 14% in different ethnic groups) lacks the enzyme that O-demethylates codeine to generate morphine.³² Thus, if a child fails to show an analgesic effect from standard dosing of codeine, consideration should be given to substituting a different opioid, in order to circumvent this pharmacogenetic barrier. Dosage guidelines for codeine and other opioid analgesics can be found in the table.

Methadone also is available as an oral elixir and, because of its long half life, can provide excellent analgesia even with infrequent dosing. It has an oral bioavailability of 60% to 90%, so dosage ranges for oral and intravenous administration are similar. Due to slow and variable clearance, methadone requires careful assessment and titrated to prevent delayed sedation.

Intravenous Opioids

With few exceptions, opioids should be administered to children either via the oral or intravenous route. Intramuscular injections should be avoided unless absolutely necessary. Many children have a tremendous fear of “shots” and if offered an injection for pain relief, will deny that they are in pain to avoid receiving a shot. Some children are willing to endure a great deal of pain if intramuscular injections are all that are offered for postoperative pain relief.

Though intermittent intravenous boluses of morphine, hydromorphone or fentanyl can provide rapid pain relief, their duration of action is short. The dosing interval for these opioids, therefore, should not be greater than every 2 to 4 hours. In order to provide a more steady analgesic effect, continuous opioid infusions and patient- or nurse- controlled analgesia (PCA or NCA) are commonly used to circumvent the the fluctuations in plasma concentrations. Intermittent dosing with the longer-acting opioid, methadone, can be very effective, but should not be prescribed by those without specific knowledge of the challenges inherent in the safe prescribing of this drug. Meperidine is generally not recommended when other opioids are available because of the potential for seizures and other toxicities due to its metabolite, normeperidine.

Continuous Opioid Infusions

For toddlers and children, commonly recommended initial morphine infusion rates are roughly 0.025 mg/kg/hr.³³ Due to the pharmacokinetic and pharmacodynamic factors described above, initial infusion rates in newborns are much lower and range from 0.005 to 0.01 mg/kg/hr. Cardiorespiratory monitoring is required for infants less than 3 months of age and adjustment of these rates should be based on clinical signs of either inadequate pain relief or increased somnolence.

Patient Controlled Analgesia

PCA is widely used for postoperative pain relief in both children and adults. With appropriate preoperative teaching and encouragement, children as young as 6 to 7 years of age can independently use the PCA pump to provide good postoperative pain relief.³⁴ Children between the ages of 4 and 6, however, generally require encouragement from their parents and nursing staff to push the button before anticipated painful movements or procedures. Even with encouragement, the failure rate among 4 and 5 year olds with PCA appears quite high. For younger children, NCA has recently gained popularity to permit small titrated dosing of opioids for infants and children unable to use the PCA button.³⁵

Typical Starting Parameters for PCA

Drug	Bolus dose (mcg/kg)	Continuous rate (mcg/kg/hour)	4 hour limit (mcg/kg)
Morphine	20	4-15	300
Hydromorphone	5	1.3	60
Fentanyl	0.25	0.15	4

Lockout interval = 5 to 7 minutes. The lockout interval is the period during which the PCA unit is refractory to further demands by the patient, and is necessary to prevent patients from taking an additional dose before appreciating the effect of the preceding dose.



PCA may be administered either alone or in conjunction with a low-dose continuous infusion. Initial parameters for the most commonly used agents can be found in the table (see above), Typical Starting Parameters for PCA. Morphine, hydromorphone and fentanyl have all been used and there are no data to suggest that one is inherently better than another. There is large individual variation across drugs, however, and it may be necessary to shift from one to another to find the most beneficial agent. Morphine has been the most extensively studied in children and often is tried first. Basal infusions improve sleep quality, but have been associated with episodes of hypoxemia when used for postoperative pain management in children.³⁶ One solution for this has been to combine PCA in bolus-only mode with round-the-clock administration of NSAIDs and/or acetaminophen. For children with acute pain associated with chronic illness, most of whom have developed some tolerance to opioid analgesics, a larger basal infusion is preferred to adequately control disease-related pain. For tumor-related pain or palliative care, roughly two-thirds of the overall requirement is provided from the basal infusion.

Although PCA is widely available in the U.S., it is useful to have options when considering strategies for the management of inpatients with acute severe pain. By delivering very small boluses of drug at a very short interval, PCA eliminates the problem of fluctuating effects associated with bolus injections of a short-acting opioid at an interval of several hours. The use of a simple regimen involving intravenous methadone can accomplish the same outcome.³⁷ In this approach, loading doses (usually 0.1 to 0.2 mg/kg) are given and the nursing staff evaluates pain at intervals not exceeding 4 hours (reverse "PRN" method). The drug is administered via a "sliding scale". If the pain is rated as severe, 0.07 mg/kg is administered; 0.05 mg/kg is given for moderate pain or 0.03 mg/kg if the pain is considered mild. This method can be safe and effective, but is dependent on an available, well-trained staff.

Children who have chronic pain related to cancer or other serious illness can be treated with long-term opioid therapy, typically with oral or transdermal delivery. The guidelines to optimize outcomes mirror those of adults.

Local Anesthetics and Regional Anesthesia

Topical anesthetics

Until recently local anesthetics had to be injected into the skin to be effective. A number of new topical anesthetics have recently become widely available to provide pain relief prior to the many anticipated needle-stick procedures that children must undergo in the first 6 years of life.³⁸

Eutectic Mixture of Local Anesthetics (EMLA)

Eutectic mixtures of local anesthetics such as lidocaine/prilocaine and lidocaine/tetracaine are effective in reducing pain from dermatologic procedures, venipuncture, etc. The mixture of lidocaine/prilocaine (EMLA) was one of the first topical anesthetics commercially available for use on intact skin and has been the most extensively used and studied.³⁹ The physico/chemical feature of this type of mixture permits a higher effective concentration at the stratum corneum and increases the rate of uptake.

Clinical trials have shown effectiveness of EMLA in reducing the pain or distress of a number of common pediatric procedures including venous cannulation, venipuncture, lumbar puncture, circumcision, urethral meatotomy and adhesion release, immunizations, arterial cannulation, dermatologic procedures, allergy testing, accessing implanted central venous access catheters, and laceration repair. EMLA must be applied in a thick layer and is most effective if left undisturbed for at least 90 to 120 minutes. Allowing time for the cream to be fully effective may be difficult in busy ambulatory clinics, and new topical approaches, including patch delivery, heat-enhanced delivery, and other drug formulations have been developed in an effort to improve the outcomes obtained with EMLA.^{38,39}

Iontophoresis

Other techniques also have been developed for the same purpose: prompt local anesthesia in a relatively small area. One of these is iontophoresis of lidocaine (Numby Stuff™), which employs an electrical field to drive local anesthetics in their charged ionic form across the stratum corneum.⁴⁰ Iontophoresis can provide deeper levels of analgesia with a much shorter onset time (10 to 25 minutes), which has made it popular for use prior to Procedural Sedation in the emergency department. Though there is a mild tingling sensation during drug delivery, this is generally well tolerated. The duration of application to achieve sufficient analgesia is dependent on the amount of current used. With higher currents (*i.e.*, 4 mAmps), there is more tingling of the skin, but analgesia can be achieved in approximately 10 minutes. Longer application times (approximately 25 to 30 minutes) are needed when lower currents are used, but the tingling sensation can be made almost undetectable.

Liposomal lidocaine

Lidocaine can be dispersed in liposomes to facilitate transcutaneous delivery. This formulation (ELA-max) is available as an over-the-counter medicine and can be massaged into the skin without occlusion, providing skin anesthesia within 30 minutes. Several recent studies suggest that its analgesic effects may be equivalent to EMLA, even with this shorter application time.⁴¹



Vapocoolant spray

Vapocoolant sprays (primarily ethyl chloride) have been used for the treatment of myalgic pain since the 1950s. Recent studies have suggested that these sprays can also provide inexpensive, rapid and effective analgesia for short duration procedures, such as venipuncture and immunization.⁴² The vapocoolant can both be sprayed directly onto the skin or onto a cotton ball and then applied to the injection site for 15 seconds. The procedure is then performed as quickly as possible while the transient cooling effects are still present. The advantages of this technique are the rapid onset time and the low cost. Skin reactions have been noted with agents containing ethyl chloride, but because of the rapid evaporation of these agents, appear to be quite rare.

Infiltration of Local Anesthetics

When topical local anesthesia is not feasible because of time constraints in urgent or emergent situations, infiltration of 1% lidocaine to an intended puncture site can significantly reduce the pain associated with venous or arterial cannulation. Intradermal injection pain can be significantly lessened by the use of a smaller needle, and buffering of the local anesthetic with the addition of sodium bicarbonate (4 ml lidocaine mixed with 1 ml sodium bicarbonate). A bioinjector has also recently been introduced which uses compressed CO₂ to inject the lidocaine rapidly beneath the skin. Clinical experience has shown that hydration decreases the pain of local anesthesia. One to 2 glasses of water (if the patient is able to drink) will help the initial pain of the block.

Regional Anesthesia and Analgesia

Regional anesthetic techniques are commonly used in children to decrease general anesthetic requirements and aid in postoperative pain management. As with adults, multimodal analgesia techniques using combinations of local anesthetics, nonsteroidal anti-inflammatory agents and opioids provide optimal analgesia. In young children, single-shot caudal injections of local anesthetics are easy to perform for outpatient and short-stay surgeries. Continuous epidural analgesia via indwelling catheters can provide excellent postoperative analgesia for infants and children of all ages undergoing more extensive abdominal and lower extremity procedures.

Procedural Sedation

In the last 10 years, as the number of nonoperative diagnostic and therapeutic procedures for children have grown, pediatric caregivers have been searching for ways to make these procedures more acceptable to children and their parents. The increasing use of sedatives and analgesics for children grew out of the popularity of the use of minimal sedation (anxiolysis) in adults to make invasive procedures more comfortable and less stressful. The development of pediatric sedation services and institutional sedation protocols has increased both the safety and availability of sedation and analgesia for children undergoing a number of painful procedures.⁴³

Persistent Pain in Children

Persistent pain is much less prevalent in children than adults, but episodic headaches, abdominal pain and chest pain are seen relatively commonly in pediatric clinics. Specific information about treatment for these types of pain will be included in subsequent modules in this CME series. Children with chronic medical disease (e.g., cancer, arthritis, cystic fibrosis, sickle cell anemia) can experience a significant amount of pain associated with both their underlying disease and the procedures that are performed to treat it. They deserve not only access to adequate pain medication, but also psychological support to help them continue to learn and grow as they should.

Summary

Children of all ages deserve compassionate and effective pain treatment. Analgesics should be used in effective doses, but pain and symptom management and supportive care should not be limited to medical therapies alone. Healthcare practitioners should recognize that pain treatment and prevention is essential even when children are too young or cognitively unable to report the extent and severity of their pain. Fear, anxiety and even phobias can develop as a result of painful experiences long before children can express them. Concerted efforts should be undertaken to reduce or eliminate pain whenever possible for routine medical procedures in children. This includes the use of topical local anesthetics for immunizations and phlebotomy, as well as penile nerve block or EMLA prior to circumcision. Appropriate pain management services should be available for children with chronic or recurrent pain associated with medical disease or injury. This includes all of the current modalities for treating pain in adults, as well as sedation or anesthesia for invasive procedures. Because of their lower pain thresholds and poor central modulation, infants and young children often require sedation or general anesthesia in order to undergo procedures that may be performed with minimal or no analgesia in adults.

Recommendations from the American Pain Society and the American Academy of Pediatrics:⁵

- Expand knowledge about pediatric pain and pediatric pain management principles and techniques.
- Provide a calm environment for procedures that reduce distress-producing stimulation.
- Use appropriate pain assessment tools and techniques.
- Anticipate predictable painful experiences, intervene, and monitor accordingly.
- Use a multimodal approach (pharmacologic, cognitive, behavioral, and physical) to pain management and use a multidisciplinary approach when possible.
- Involve families and tailor interventions to the individual child.
- Advocate for the effective use of pain medication for children to ensure compassionate and competent management of their pain.



References

- Andrews K, Fitzgerald M. Cutaneous flexion reflex in human neonates: a quantitative study of threshold and stimulus-response characteristics after single and repeated stimuli. *Dev Med Child Neurol.* 1999;41:696-703.
- Taddio A, Katz J, Illersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet.* 1997;349: 599-603.
- Schechter NL. The undertreatment of pain in children: an overview. *Pediatr Clin North Am.* 1989;36:781-794.
- Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med.* 1987;317:1321-1329.
- Committee on Psychosocial Aspects of Child and Family Health, American Academy of Pediatrics; Task Force on Pain in Infants, Children, and Adolescents, American Pain Society. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics.* 2001;108(3):793-797.
- Grunau RV, Johnston CC, Craig KD. Neonatal facial and cry responses to invasive and non-invasive procedures. *Pain.* 1990;42:295-305.
- Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. *Clin J Pain.* 1996;12:13-22.
- Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. *Neonatal Netw.* 1993;12:59-66.
- Merkle SI, Shayevitz JR, Voepel-Lewis T, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs.* 1997;23:293-297.
- von Baeyer CL. Children's self-report of pain intensity: what we know, where we are headed. *Pain Res Manag.* 2009;14(1):39-45.
- Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein M, Schwartz P. *Essentials of Pediatric Nursing.* 5th ed. St. Louis: Mosby; 2001:1301.
- Beyer JE, Denyes MJ, Villarruel AM. The creation, validation, and continuing development of the Oucher: a measure of pain intensity in children. *J Pediatr Nurs.* 1992;7:335-346.
- Hester NO, Foster R, Kristensen K. Measurement of pain in children: generalizability and validity of the Pain Ladder and the Poker Chip Tool. In: Tyler DC, Krane EJ, eds. *Pediatric Pain. Vol 15. Advances in Pain Research and Therapy.* New York: Raven Press Ltd.; 1990:70-84.
- McGrath P, Gillespie J. Pain Assessment in Children and Adolescents. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment.* New York: Guilford Press; 2001:97-117.
- Varni JW, Thompson KL, Hanson V. The Varni-Thompson pediatric pain questionnaire I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. *Pain.* 1987;28:29-38.
- Children's comprehensive pain questionnaire [CCPQ](1984). Ross DM; Ross SA. In: McGrath PA. (1990). *Pain in children: Nature, assessment, and treatment.* New York: Guilford Press. pg.68-70, 392-400.
- Walco GA, Halpern SL, Conte PM. Pain in Infants and Children. In: Tollison CD, Satterthwaite JR, Tollison JW, eds. *Practical Pain Management.* Philadelphia: Lippincott Williams & Wilkins; 2002:748-759.
- Tateishi T, Nakura H, Asoh M, et al. A comparison of hepatic cytochrome P450 protein expression between infancy and postinfancy. *Life Sci.* 1997;61:2567-2574.
- van den Anker JN. Pharmacokinetics and renal function in preterm infants. *Acta Paediatr.* 1996;85:1393-1399.
- Martin RJ, DiFiore JM, Jana L, et al. Persistence of the biphasic ventilatory response to hypoxia in preterm infants. *J Pediatr.* 1998;132:960-964.
- Cohen G, Malcolm G, Henderson-Smart D. Ventilatory response of the newborn infant to mild hypoxia. *Pediatr Pulmonol.* 1997;24:163-172.
- Allameh A, Vansoun EY, Zarghi A. Role of glutathione conjugation in protection of weanling rat liver against acetaminophen-induced hepatotoxicity. *Mech Ageing Dev.* 1997;95:71-79.
- Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology.* 2002;96:1336-1345.
- Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mg.kg-1) rectal acetaminophen in children. *Can J Anaesth.* 1995;42:982-986.
- Birmingham PK, Tobin MJ, Henthorn TK, et al. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. *Anesthesiology.* 1997;87:244-252.
- Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med.* 2002;347:1094-1103.
- Szer IS, Goldenstein-Schainberg C, Kurtin PS. Paucity of renal complications associated with nonsteroidal anti-inflammatory drugs in children with chronic arthritis. *J Pediatr.* 1991;119:815-817.
- Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics.* 1999;104(4):e.
- Vetter TR, Heiner EJ. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine. *J Clin Anesth.* 1994;6:110-113.
- Houck CS, Wilder RT, McDermott JS, Sethna NF, Berde CB. Safety of intravenous ketorolac therapy in children and cost savings with a unit dosing system. *J Pediatr.* 1996;129:292-296.
- Anand KJ, Anderson BJ, Holford NH, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth.* 2008;101(5):680-689.
- Caraco Y, Sheller J, Wood AJ. Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J Pharmacol Exp Ther.* 1999;290:413-422.
- Esmail Z, Montgomery C, Courtrn C, Hamilton D, Kestle J. Efficacy and complications of morphine infusions in postoperative paediatric patients. *Paediatr Anaesth.* 1999;9:321-327.
- Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. *J Pediatr.* 1991;118:460-466.
- Monitto CL, Greenberg RS, Kost-Byerly S, et al. The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. *Anesth Analg.* 2000;91:573-579.
- McNeely JK, Trentadue NC. Comparison of patient-controlled analgesia with and without nighttime morphine infusion following lower extremity surgery in children. *J Pain Symptom Manage.* 1997;13:268-273.
- Berde CB, Beyer JE, Bournaki MC, Levin CR, Sethna NF. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr.* 1991;119:136-141.
- Zempsky WT. Pharmacologic approaches for reducing venous access pain in children. *Pediatrics.* 2008;122 Suppl 3:S140-153.
- Yamada J, Stinson J, Lamba J, Dickson A, McGrath PJ, Stevens B. A review of systematic reviews on pain interventions in hospitalized infants. *Pain Res Manag.* 2008;13(5):413-420.
- Irsfeld S, Klement W, Lipfert P. Dermal anaesthesia: comparison of EMLA cream with iontophoretic local anaesthesia. *Br J Anaesth.* 1993;71:375-378.
- Eichenfield LF, Funk A, Fallon-Friedlander S, Cunningham BB. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. *Pediatrics.* 2002;109:1093-1099.
- Reis EC, Jacobson RM, Tarbell S, Weniger BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. *Pediatr Ann.* 1998;27:375-386.
- Krauss B, Green SM. Procedural sedation and analgesia in children. *Lancet.* 2006;367(9512):766-780.