Pharmacokinetics and Pharmacodynamics of Analgesics and Adjuvants in Infants, Children, and Adolescents

Developmental Pharmacology

Developmental Considerations in Children

Rational and effective administration of medications for children requires a fundamental understanding and integration of the role of ontogeny in the disposition and actions of drugs. Dosing of analgesic medications for pediatric patients is dependent on the interplay between pharmacokinetics (PK), pharmacodynamics (PD), and pharmacogenomics (PG). There is much debate concerning the methodology employed to adjust PK parameters to body size. Traditionally, empirical approaches to drug dosing have been based on using either body weight or body-surface area. However, the use of linear per kilogram and surface area models have generally been considered inappropriate for scaling small children to adults, and a non-linear relationship between weight and drug elimination capacity is now widely accepted. The consideration of accurate pharmacological and pharmacokinetic data for pediatric dosing may involve the use of cumbersome mathematical analysis in order to obtain a rational, safe, and effective dose. However, the log of basal metabolic rate plotted against the log of body weight in all species studied produces a straight line with a slope of 0.75, and the use of dosing equations has largely been replaced by adjustment (or normalization) of the drug dose for either body weight or body-surface area (Anderson and Holford 2008; Anderson and Meakin 2002).

The pharmacokinetics and pharmacodynamics of analgesics change during development with profound changes over the first few months of life (Table 20.1). Most current age-specific dosing requirements are based on the known influence of ontogeny on the disposition of drugs. Developmental changes in physiology produce many of the age-associated changes in the absorption, distribution, metabolism, and excretion of drugs that culminate in altered pharmacokinetics and thus serve as the determinants of age-specific dose requirements (Berde and Sethna 2002).
Little information exists about the effect of human ontogeny on interactions between drugs and receptors and the consequence of these interactions (i.e., pharmacodynamics of agents).

Age-associated changes in body composition and organ function are dynamic and can be discordant during the first decade of life. Generally, the rate at which most drugs are absorbed is slower in neonates and young infants (<3 months of age) than in older children; thus, the time required to achieve maximal plasma levels of most drugs is prolonged in the very young. Age-dependent changes in body composition alter the physiologic spaces into which a drug is distributed. The relatively larger extracellular and total body water spaces in neonates and young infants as compared with adults, coupled with adipose stores with a higher ratio of water to lipid, result in lower plasma levels of drugs in these compartments when the drugs are administered in a weight-based fashion (Kearns et al. 2003).

The composition and amount of circulating plasma proteins (e.g., albumin and \(\alpha_1\)-acid glycoprotein) are also likely to influence the distribution of highly protein-bound drugs. A reduction in the quantity of total plasma proteins (albumin and \(\alpha_1\)-acid glycoprotein in neonate and young infant. Presence of fetal albumin and increase in bilirubin and free fatty acids. Increased free fraction of drug and availability of active moieties in drugs that are highly-protein bound. Potential for overdose or toxicity.

<table>
<thead>
<tr>
<th>System</th>
<th>Age-related changes</th>
<th>Affect on pharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition/physiologic spaces</td>
<td>Larger extracellular and total body water spaces in neonates; Adipose stores with higher ratio of water to lipid.</td>
<td>Lower plasma levels of drugs in these compartments when given in weight-based dosing regimen.</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>Decrease in quantity of total plasma proteins (albumin and (\alpha_1)-acid glycoprotein in neonate and young infant. Presence of fetal albumin and increase in bilirubin and free fatty acids.</td>
<td>Increased free fraction of drug and availability of active moieties in drugs that are highly-protein bound. Potential for overdose or toxicity.</td>
</tr>
<tr>
<td>GI absorption</td>
<td>Relatively elevated intragastric pH (&gt;4) and less gastric secretion in the neonate. Immature passive and active intestinal transport immature until age 4 months. Immature conjugation and transport of bile salts. Greater number of high-amplitude pulsatile rectal contractions.</td>
<td>Altered bioavailability of drugs given enterally. Enhanced expulsion of rectally administered drugs leading to decreased absorption.</td>
</tr>
<tr>
<td>Hepatic drug-metabolizing activity</td>
<td>Delayed maturation of hepatic drug-metabolizing enzyme activity. Immature expression of phase I enzymes (cytochrome (P_{450}) isozymes) and phase II conjugation enzymes (e.g., glucuronosyltransferases) in neonates and infants.</td>
<td>Decreased metabolic clearance of agents. Decreased infusion rates or an increase in the dosing interval (decreased frequency of dosing).</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Reduced skeletal muscle blood flow and inefficient muscular contractions in the neonate. Higher density of skeletal muscle capillaries.</td>
<td>Reduced rate of intramuscular (IM) absorption vs. higher rate of absorption via capillaries leads to relatively more efficient IM absorption in neonates.</td>
</tr>
<tr>
<td>Renal function</td>
<td>Decreased glomerular filtration rate, renal blood flow, and tubular secretion in the neonate and young infant.</td>
<td>Accumulation of renally-excreted drugs or active metabolites. Decreased infusion rates or increased dosing intervals (decreased frequency of administration).</td>
</tr>
</tbody>
</table>
the brain may alter the cerebrospinal fluid–brain and blood–brain concentration ratios and drug partitioning independent of the permeability of the blood–brain barrier (Berde and Sethna 2002).

During the neonatal period, intragastric pH is relatively elevated (>4) consequent to reductions in both basal acid output and the total volume of gastric secretions. Gastric emptying and intestinal motility are the primary determinants of the rate at which drugs are presented to and dispersed along the mucosal surface of the small intestine. Both passive and active transport are fully mature in infants by approximately 4 months of age. Developmental differences in the activity of intestinal drug-metabolizing enzymes that can markedly alter the bioavailability of drugs are incompletely characterized. Immature conjugation and transport of bile salts into the intestinal lumen result in low intraduodenal levels despite the presence of blood levels that exceed those of adults (Kearns et al. 2003).

Reduced skeletal-muscle blood flow and inefficient muscular contractions may reduce the rate of intramuscular absorption of drugs in neonates, off-set by the relatively higher density of skeletal-muscle capillaries in infants than in older children. Thus, the evidence supports the concept that intramuscular absorption of specific agents (e.g., amikacin) is more efficient in neonates and infants than in older children. The bioavailability of extensively metabolized compounds administered rectally may be enhanced in neonates and very young infants due to developmental immaturity of hepatic metabolism rather than to enhanced mucosal translocation. However, infants have a greater number of high-amplitude pulsatile contractions in the rectum than do adults, which can enhance the expulsion of solid forms of drugs, effectively decreasing the absorption of drugs such as acetaminophen (Kearns et al. 2003).

Delayed maturation of drug-metabolizing enzyme activity may account for the marked toxicity of drugs in infants and young children. Important developmental changes in the biotransformation of drugs prompt the need for age-appropriate dose regimens for many drugs commonly used in children. The developmental expression of phase I enzymes, such as the P_{450} cytochromes, changes dramatically during early childhood (Lacroix et al. 1997; Sonnier and Cresteil 1998). The ontogeny of the conjugation reactions (i.e., those involving phase II enzymes) is less well established than the ontogeny of reactions involving phase I enzymes. Individual isoforms of glucuronosyltransferase (UGT) have unique maturational profiles. The glucuronidation of acetaminophen (a substrate for UGT1A6 and, to a lesser extent, UGT1A9) is decreased in newborns and young children as compared with adolescents and adults (Miller et al. 1976). Glucuronidation of morphine (a UGT2B7 substrate) can be detected in premature infants as young as 24 weeks of gestational age (Barrett et al. 1996). The clearance of morphine from plasma is positively correlated with post-conceptional age and increases fourfold between 27 and 40 weeks post-conceptional age, thereby necessitating corresponding increases in the dose of morphine to maintain effective analgesia (Scott et al. 1999).

A consistent observation in clinical studies of drugs metabolized in the liver is an age-dependent increase in plasma clearance in children younger than 10 years of age, which necessitates relatively higher weight-based dosing. The mechanisms underlying these age-related increases in plasma drug clearance are largely unknown. This higher rate of drug metabolism has been historically attributed to the larger liver mass/kg body weight (Blanco et al. 2000); however, it is unlikely that the greater drug clearance in infants and young children can be attributed solely to a disproportionate increase in liver mass, given that the weight of the liver as a percentage of total body mass reaches a maximum between 1 and 3 years of age and declines to adult values during adolescence (Kearns et al. 2003).

Maturation of renal function is a dynamic process that begins during fetal organogenesis and is complete by early childhood. The glomerular filtration rate, renal blood flow, and tubular secretion increase rapidly during the first 2 weeks of life and then rises steadily until adult values are reached at 8–12 months of age (Berde and Sethna 2002). Developmental changes in renal function can dramatically alter the plasma clearance of
compounds with extensive renal elimination and thus constitute a major determinant of the age-appropriate selection of a dose regimen in young children.

**Pharmacological Agents for Chronic Pain Management**

**Nonopioid Primary Analgesics [Acetaminophen, Salicylates, and Nonsteroidal Anti-inflammatory Drugs (NSAIDs)]**

The peripheral and centrally acting primary nonopioid analgesics are medications that are useful for the management of acute, recurrent pain and chronic pain (Table 20.2). These agents may be used for postsurgical pain, trauma, arthritis, headache, and cancer-related pain. There is a wide variety of variability of response to these medications between individuals, and the benefits/risks of these agents for chronic use is an area of evolving research (Munir et al. 2007).

**Acetaminophen**

Acetaminophen (APAP) is a very popular analgesic for infants and children and is commonly used for the management of acute and chronic pain in adults and children. It is generally well-tolerated with demonstrated analgesia compared to placebo. The primary mechanism of action is the central inhibition of the cyclooxygenase enzymes in the central nervous system leading to an inhibition of prostaglandin synthesis. There is no clinically relevant inhibition of prostaglandin synthesis in the peripheral nervous system; hence, acetaminophen has no significant anti-inflammatory or hematological (platelet) effects. The analgesic and antipyretic potency of APAP is similar to aspirin. Acetaminophen suppresses neuronal excitability both centrally and peripherally (Anderson 2008; Graham and Scott 2005). The route of administration determines the dose to be given with oral dosing of 10–15 mg/kg every 4–6 h to a maximum dose of 100 mg/kg/day or 4,000 mg/day. Acetaminophen is available as a rectal suppository (180, 325, and 650 mg); however, rectal absorption can often be erratic and the effective dose for analgesia is higher than with oral dosing (20–35 mg/kg rectally vs. 10–15 mg/kg orally) (Birmingham et al. 1997). Acetaminophen does not cause gastric mucosal irritation and is well-tolerated orally. It also has no hematological side-effects (no anti-platelet activity). The major pathway for the metabolism of acetaminophen is via glucuronidation or sulfation in the liver; the minor pathway for metabolism is the mixed function oxidases. There is a toxic intermediate metabolite which is inactivated by conjugation with glutathione. Use of acetaminophen in large doses may deplete glutathione stores resulting in accumulation of this toxic metabolite potentially resulting in centrilobular hepatic necrosis (a potentially fatal disease); therefore recommended daily maximum doses should not be exceeded (James et al. 2008; Mortensen 2002). APAP is a common ingredient in many prescription and nonprescription analgesics and caution should be exercised to avoid concomitant use and potential overdose.

**ASA (Acetylsalicylic Acid-[aspirin]) and Salicylate Salts**

Invented in 1897, aspirin is one of the oldest nonopioid analgesics. It was very commonly used for children and adults; however, use as an analgesic has been largely replaced by nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Pediatric dosing is 10–15 mg/kg orally every 4–6 h. The potential association between aspirin use and Reye syndrome in young children with a concomitant viral illness has led to avoidance of this drug for routine use in children (Cron et al. 1999). In 2003, the US Food and Drug Administration ordered the placement of warning labels on all salicylates describing the potential for the development of Reye syndrome with use.

The salicylate salts, choline magnesium trisalicylate and salsalate, are compounds related to aspirin and are used as analgesics in the setting of patients with potential for the development of coagulopathies. Therapeutic doses of these agents do not effect bleeding time or platelet aggregation tests (Stuart and Pisko 1981; Sweeney and Hoernig 1991). Therefore, these medications are often useful in patients with oncologic diseases...
and pain in which the patient may benefit from analgesia without potential for further coagulopathies from medication. Choline magnesium trisalicylate is sometimes used for pediatric patients with oncologic disease, and the typical pediatric dosing regimen is 25 mg/kg given twice daily.

### Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The nonsteroidal anti-inflammatory drugs (NSAIDs) are effective analgesics for chronic pain that is associated with inflammation as these agents have pharmacological properties that are both analgesic and anti-inflammatory. These agents have been shown in many clinical trials to be moderately effective for analgesia versus placebo. These agents are most effective for mild pain and often used in combination with opioids for moderate pain. These agents are structurally distinct with three major families of agents (carboxylic acids, pyrazoles, and oxicams) but exhibit a similar mechanism of action; NSAIDs are often referred to as peripherally acting nonopioid analgesics. All of the NSAIDs inhibit the enzyme cyclooxygenase (COX) resulting in a decreased production of prostaglandins.

#### Table 20.2 Peripherally acting nonopioid analgesics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pediatric dose</th>
<th>Adult dose</th>
<th>Maximal daily adult dose (mg)</th>
<th>Plasma half-life (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophena</strong></td>
<td>10–15 mg/kg q 4–6 h</td>
<td>500–1,000 mg q4–6 h</td>
<td>4,000</td>
<td>2–3</td>
<td>Do not exceed 100 mg/kg/day. Available as rectal suppository.</td>
</tr>
<tr>
<td><strong>Salicylates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirina</td>
<td>10–15 mg/kg q 4–6 h</td>
<td>500–1,000 mg q4–6 h</td>
<td>4,000</td>
<td>0.25</td>
<td>Do not use for children under 12 years of age with possible viral illness due to potential for Reye syndrome. Available as rectal suppository.</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate</td>
<td>25 mg/kg BID</td>
<td>1,000–1,500 mg q12 h</td>
<td>2,000–3,000</td>
<td>9–17</td>
<td>Aspirin-like compound that does not increase bleeding time.</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofena</td>
<td>5–10 mg/kg q6 h</td>
<td>200–400 mg q4–6 h</td>
<td>2,400</td>
<td>2–2.5</td>
<td>Most commonly used NSAID in the USA. Also available as 100 mg/5 mL suspension.</td>
</tr>
<tr>
<td>Naproxena</td>
<td>5–10 mg/kg BID</td>
<td>500 mg load f/b 275 mg q6–8 h</td>
<td>1,500</td>
<td>12–15</td>
<td>Also available as 125 mg/5 mL suspension.</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2–4 mg/kg q8 h</td>
<td>25 mg q8–12 h</td>
<td>200</td>
<td>2</td>
<td>GI and CNS side effects are common.</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>10–20 mg/kg daily</td>
<td>600 mg q12–24 h</td>
<td>1,200</td>
<td>2–69</td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.125–0.25 mg/kg daily</td>
<td>7.5–15 mg q24 h</td>
<td>15</td>
<td>15–20</td>
<td>7.5 mg/ 5 mL suspension.</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.2–0.4 mg/kg/day (max 15 mg/day)</td>
<td>20–40 mg q24 h</td>
<td>40</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1–2 mg/kg/dose</td>
<td>50 mg q8 h</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etodolac</td>
<td>15–20 mg/kg/day q12 h</td>
<td>300–400 mg q8–12 h</td>
<td>1,000</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>50 mg BID (for children 10–25 kg, 100 mg BID for children &gt;25 kg.)</td>
<td>200–400 mg q12–24 h</td>
<td>400</td>
<td>11</td>
<td>Selective COX-2 inhibition.</td>
</tr>
</tbody>
</table>

*BID twice a day, NSAIDs: nonsteroidal anti-inflammatory drugs, COX: cyclo-oxygenase

*aFDA-approved drugs for children
agents involved in the peripheral response to a noxious stimulus and the inflammatory and nociceptive events which accompany injury and disease, thereby suppressing neuronal excitability peripherally (Tobias 2000; Vane 1971).

There are two isoforms of the COX enzyme: COX-1, which is found constitutively in platelets, kidneys, the GI tract, and other tissues, and the COX-2 isozyme, which is found constitutively in the kidneys and central nervous system and whose formation is induced in the peripheral tissues by noxious stimuli that cause inflammation and pain (Morita 2002). Most of the NSAIDs are nonselective inhibitors of the COX isozymes and may vary in their relative COX-1 and COX-2 selectivity. While these agents principally are peripherally acting analgesics, there is evidence of a central mechanism of action (in the brain and spinal cord) as well involving the inhibition of prostaglandin synthesis, activation of endogenous opioid peptides, and serotonergic-mediated events (Malmberg and Yaksh 1992).

These agents have a widely varying chemical composition and are structurally distinct from one another; however, there is good clinical evidence that nonselective NSAIDs are comparable in efficacy to each other. There may be a great interpatient variability in the analgesic response to a particular NSAID, but no structure–activity relationship exists, so the efficacy of one agent for a particular patient vs. another cannot be fully understood at present. Thus, a patient who does not respond to a NSAID from one chemical class is just as likely to respond to another NSAID from the same chemical class as a NSAID from another chemical class. Therefore, when considering the use of a NSAID for chronic pain, if the patient does not respond to a particular agent, then the provider should consider a trial with an alternative NSAID agent.

The use of NSAIDs is limited by the analgesic ceiling effect of these medications in which there is no additional analgesic effect but an increase in toxicity with dose escalation. These agents do not produce physical or psychological dependence with use and are also antipyretic (Munir et al. 2007). NSAIDs are the mainstay of treatment for pain associated with pediatric rheumatic diseases such as juvenile idiopathic arthritis (Kimura and Walco 2007). They provide effective analgesia in many patients and are commonly used as first-line agents. NSAIDs that are approved by the US FDA for use in pediatric patients include ibuprofen, naproxen, oxaprozin, etodolac SR, meloxicam, indomethacin, and celecoxib (Kimura and Walco 2007). Ibuprofen remains the most commonly used NSAID for pediatric pain; it is available as a 100 mg chewable tablet, 200 mg tablet, and 100 mg/5 cc oral suspension, and the routine dose for children is 5–10 mg/kg orally every 6 h with a recommended maximum dose of 40 mg/kg or 2,400 mg/day.

There are many potentially significant adverse events that may occur with prolonged use of NSAIDs. Patients may develop gastrointestinal (dyspepsia, bleeding, and peptic ulcer formation through inhibition of protective prostaglandin formation) and hematologic [platelet inhibition due to reversible inhibition of thromboxane synthesis (Niemi et al. 1997)] adverse events. Dyspepsia may occur early in therapy, and the provider should strongly encourage the patient to take these medications with food to minimize this potential effect. GI ulceration, bleeding, or perforation can occur at any time during therapy with NSAIDs, often without any warning symptoms (Garcia Rodriguez and Barreales 2007). Children receiving NSAIDs as treatment for chronic pain and disease are less likely than adults to have GI adverse effects.

NSAIDs may also lead to inability for platelets to aggregate due to reversible inhibition of thromboxane synthesis, and use of anticoagulants, coagulopathy, and thrombocytopenia is a relative contraindication for the use of NSAIDs. These agents may also be associated with bone marrow suppression (Nuki 1990). Renal dysfunction may occur with NSAID use due to inhibition of prostaglandin-mediated intrarenal vasodilatation during hypovolemia or reduced renal blood flow (Munir et al. 2007). NSAIDs can produce liver damage, and this is usually detected as an elevation in liver enzymes. Monitoring of liver enzymes, bilirubin, and markers of kidney function should be considered with prolonged use of these agents for chronic pain conditions. Liver disease
or elevated liver function tests (LFTs) are relative contraindications for the use of NSAIDs (Rubenstein and Laine 2004). Bronchospastic NSAID-exacerbated respiratory disease (ERD) has been reported in children and adults, and NSAID ERD is a concern in one of three teenagers with severe asthma and coexisting nasal disease (Sturtevant 1999). Pseudoporphyria has been associated with the chronic use of NSAIDs in some children (Lang and Finlayson 1994).

**Opioid Analgesics**

Opioid analgesics are very commonly used in the analgesic management of children of all ages, from neonates to adolescents. These agents are often added to nonopioid analgesics to manage cancer-related pain and potentially noncancer chronic pain. Opioid analgesics will decrease or modify the perception of pain in the central nervous system, and these medications are titrated to effect as they have no ceiling effect for dose. Opioids provide analgesia principally via the mu (μ), kappa (κ), and delta (δ) opioid receptors by mimicking the actions of the endogenous opioid peptides resulting in membrane hyperpolarization and analgesia. These receptors are principally located in the brain and spinal cord, but they can also be found in peripheral nerve cells and immune cells (Snyder and Pasternak 2003). Endogenous and exogenous opioid compounds will bind to these receptors. Inter-individual variability in the response to opioids may be due in part to genetic polymorphisms that effect opioid binding and efficacy. The opioids that are most commonly used in the management of chronic pain in children are mu agonists; these agents include morphine, hydromorphone, fentanyl, meperidine, and methadone (Table 20.3). Mixed agonist–antagonists agents are used much less commonly; most of these drugs act as agonists or partial agonists at the kappa and sigma receptors but are antagonists at the mu receptor. Mixed agonist/antagonist agents in common use include butorphanol, buprenorphine, and nalbuphine.

Opioid receptors are found both presynaptically and postsynaptically, and are coupled to guanine nucleotide (GTP) binding regulatory proteins (G proteins). These receptors regulate via transmembrane signaling mechanisms of the inward K⁺ current, resulting in membrane hyperpolarization as well as decreased cyclic adenosine monophosphate production (cAMP), increased nitric oxide (NO) synthesis, and the production of 12-lipoxygenase metabolites. The opioid-sparing effect of concomitant use of NSAIDs is likely due to the blockade of prostaglandin synthesis leading to greater availability of 12-lipoxygenase metabolites (Pasternak 2005; Zelcer et al. 2005). Some of the adverse effects of opioids may result from the opioid binding to stimulatory G-proteins and is antagonized by ultra-low dose naloxone infusions (Ganesh and Maxwell 2007; Maxwell et al. 2005).

Most of the opioids are biotransformed by the liver prior to excretion by the kidneys. In the liver, most of the metabolism of the opioids occurs via glucuronidation or by the microsomal mixed-functions oxidases which use the cytochrome P₄₅₀ system. The cytochrome P₄₅₀ is not fully developed at birth and does not reach maturity until approximately 3 months of age; it is likely that the immaturity of this system is responsible for the prolonged effect of a dose of an opioid in a neonate and young infant. Opioid drugs should be used cautiously in patients with significant liver or kidney disease as the metabolism and excretion will be altered potentially leading to accumulation of drug. Prodrugs (such as codeine), which are inactive and require metabolism by the liver for activity, may be ineffective in patients with liver disease.

Side effects due to the opioid agents are often dose-dependent and may involve sedation and respiratory depression in some patients. Thus, patients who are taking opioid medications for pain need to be monitored regularly for efficacy and adverse effects. There is no evidence that one opioid is more effective clinically than another, and the choice of opioid is individualized with respect to the patient’s clinical state, previous responses to the agent, and potential for side effects. Across all age groups, there is significant variability in the dose of an opioid needed to provide adequate analgesia, even in patients who are opioid-naïve. Polymorphisms in the genes that
Table 20.3  Commonly used opioid drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Equianalgesic dosing (mg)</th>
<th>Initial oral dose</th>
<th>Bioavailability (%)</th>
<th>Duration (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Parenteral</td>
<td>Adult (&gt;50 kg)(mg)</td>
<td>Children (mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Mu (µ) agonist drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>NA</td>
<td>30–60</td>
<td>0.5–1</td>
<td>15–80</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>5–10</td>
<td>0.1–0.2</td>
<td>60–80</td>
<td>3–4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15–20 mg</td>
<td>NA</td>
<td>5–10</td>
<td>0.1–0.2</td>
<td>60–80</td>
</tr>
<tr>
<td>Morphine</td>
<td>30 mg (short term)/60 mg (single dose)</td>
<td>10 mg</td>
<td>20–50</td>
<td>0.3</td>
<td>20–40</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6–8 mg</td>
<td>1.5–2 mg</td>
<td>2–4</td>
<td>0.04–0.08</td>
<td>50–70</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>NA</td>
<td>0.1 mg (100 µg)</td>
<td>NA</td>
<td>NA</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg</td>
<td>75–100 mg</td>
<td>100–150 mg</td>
<td>2–3 mg/kg</td>
<td>40–60</td>
</tr>
<tr>
<td>Methadone</td>
<td>10–20 mg</td>
<td>10 mg</td>
<td>5–10 mg</td>
<td>0.1–0.2 mg/kg</td>
<td>70–100</td>
</tr>
<tr>
<td>Weak mu (µ) agonist-monoamine reuptake inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50–100</td>
<td>1–3</td>
<td>68 (first dose), 90–100 (multiple doses)</td>
<td>3–6</td>
<td>Maximum dose is 400 mg/day or 8 mg/kg/day. Available as extended-release tablet. May lower seizure threshold in patients susceptible. Rarely associated with serotonergic syndrome.</td>
</tr>
</tbody>
</table>

APAP acetaminophen, MAO monoamine oxidase
control the mu-receptor and the melanocortin-1 receptor, as well as genes that regulate the agents of opioid metabolism (e.g., the cytochrome P$_{2D6}$ isozyme) are likely to account for some of this variability (Pasternak 2001; Pasternak 2005). It is important to obtain a pain medication history to elicit information on the efficacy and adverse effects of opioids used previously. Some patients will respond better to one opioid than another, even when the two opioids are from the same class; therefore, serial trials of opioids should be used to determine the most effective agent for the patient who is experiencing partial pain relief or significant adverse effects. Providers should administer opioid agents at regular intervals according to the predicted pharmacokinetics of the drug with “rescue” dosing for breakthrough pain. The typical “rescue” dose is 5–10% of the daily requirement of the opioid which can be given as frequently as every one hour for unrelied pain. Escalation of dosing with incorporation of the breakthrough doses is encouraged to titrate to effect or side effects. Key concepts for the use of opioids for pain management include titration to effect, a goal for steady state analgesia, anticipation and treatment of side effects, and use of equianalgesic doses when switching opioids in patients who are opioid-naïve.

Codeine, hydrocodone, and oxycodone are commonly used oral opioids to treat pain in children. The sustained-released formulations of oxycodone, hydromorphone, and morphine, as well as methadone, are more commonly used to treat chronic pain in children. Often, codeine, hydrocodone, and oxycodone are administered in combination with acetaminophen (Tylenol® with Codeine, TYLENOL® with codeine elixir, Vicodin®, Lortab®, Percocet®, and Tylox®). These agents will have similar efficacy (analgesia, cough suppression) and adverse effects (sedation, nausea, vomiting, constipation, respiratory depression) when given at equipotent dosing. Codeine, hydrocodone, and oxycodone have an oral bioavailability of approximately 60%, and achieve analgesic efficacy within 20 min after oral dosing. The elimination half-life of these agents is 2.5–4 h so they are often prescribed every 4–6 h for pain control.

Codeine has a variable bioavailability (15–80%) but also is an inactive prodrug that has analgesic efficacy only via metabolism to morphine. This metabolism is dependent on the mixed function oxidases with the cytochrome P$_{2D6}$ enzyme isomer. There are slow metabolizers of codeine (Caucasian 10%, Chinese 30%), and the drug is ineffective for these patients while 5% of the population will be ultra-rapid metabolizers with increased concentrations of morphine (Williams et al. 2001). Typically, codeine is prescribed at a dose between 0.5 and 1 mg/kg/dose. Tylenol with codeine elixir contains 120 mg of acetaminophen and 12 mg of codeine in each 5 ml (1 tsp). Tylenol #1-#4 tablets contain acetaminophen with varying amounts of codeine per tablet: Tylenol #1 (7.5 mg), #2 (15 mg), #3 (30 mg), and #4 (60 mg). The acetaminophen (APAP) will potentiate the analgesia and allows, through the opioid-sparing effects, a lower dose of opioid. However, these agents, if used beyond the recommended dose, may lead to acetaminophen toxicity, and the FDA is considering the removal of all combination APAP/opioid drugs from the US market to avoid this potential hazard.

Hydrocodone is prescribed at a dose of 0.1–0.2 mg/kg/dose and is available as an elixir or tablet combined with acetaminophen. Each 5 ml of the elixir contains 2.5 mg of hydrocodone and 167 mg of APAP. Tablets are available which contain between 2.5 and 10 mg of hydrocodone and 500–650 mg of APAP. Oxycodone is a semi-synthetic opioid with mu and kappa-receptor activity which is also prescribed at a dose between 0.1–0.2 mg/kg/dose and is most commonly available as a tablet combined with acetaminophen; Percocet® contains APAP 325 mg with 5 mg oxycodone, and Tylox® contains APAP 500 mg with 5 mg oxycodone. Oxycodone is available as an elixir (without acetaminophen) with a concentration of 1 mg/ml or 20 mg/ml. Oxycodone is also available with acetaminophen as a sustained-released tablet (OxyContin®) for use with patients with chronic pain. This sustained-release formulation allows for BID or TID dosing and should only be used for opioid-tolerant patients. If the tablet is crushed or chewed, large doses of the agent can be released resulting in potentially serious respiratory or cardiovascular injury.
Tramadol is a synthetic 4-phenyl-piperidine analog of codeine which is a racemic mixture of (+) and (−) entantiomers that is a weak mu-receptor opioid agonist and norepinephrine/serotonin reuptake inhibitor used for mild to moderate pain. It has been used in Europe for many decades and is becoming more popular in the USA. The opioid activity of tramadol results from low affinity binding of the (+) entantiomer to mu-opioid receptors. Tramadol has no affinity for the delta or kappa-opioid receptors. The (+) entantiomer inhibits serotonin uptake and has a direct serotonin-releasing action while the (−) entantiomer is an inhibitor of norepinephrine reuptake.

It is metabolized in the liver to O-desmethyltramadol by the cytochrome P\textsubscript{450} system (cytochrome P\textsubscript{450} 2D6 and cytochrome P\textsubscript{450} 3A4 isozymes). The drug undergoes extensive first-pass metabolism in the liver. Tramadol is largely eliminated by the kidney (90%) and has nausea/vomiting, dizziness, constipation, and sedation as common side effects. It should be used cautiously in patients with a history of seizure disorder or with medications that potentially lower the seizure threshold. It has also been associated with serotonergic syndrome in some patients with concomitant risk factors (Bozkurt 2005). The use of 5-HT\textsubscript{3} antagonists (e.g., ondansetron) may decrease the efficacy of tramadol via the 5-HT\textsubscript{3} receptor (De Witte et al. 2001).

In adults, oral tramadol has a bioavailability of 68% after the first dose and 90–100% after multiple doses. The time to onset is 30–60 min and the time to peak concentration is 2 h. Tramadol is supplied as a 50 mg oral tablet or as an extended-release tablet (Ultram ER\textsuperscript{®}-100, 200, or 300 mg). It can be used as a compounded liquid with stability of 30 days. The typical dose for children <50 kg is 1–3 mg/kg/dose given every 3–6 h [max dose 8 mg/kg/day] or 50–100 mg every 3–6 h in patients weighing ≥50 kg [max dose 400 mg/day]. It is recommended as a potential analgesic in step 2 of the World Health Organization’s guidelines for the treatment of patients with cancer pain (Leppert and Luczak 2005). In a study by Rose et al. for the treatment of chronic pain in children, tramadol had good efficacy and was well tolerated (Rose et al. 2003).

Potent opioids are used for the treatment of moderate to severe pain. Oral dosing is the most common route of administration; however, intravenous, subcutaneous injection/infusion, rectal dosing, and transdermal dosing options are used as needed. Morphine is the “gold standard” for pain management and is often the first-choice opioid prescribed for chronic cancer pain due to the long track record of safe use, the availability of the agent in various formulations, and its hydrophilicity. Morphine, of all the opioid agents, has been studied the most extensively in children. Morphine is metabolized in the liver principally by uridine diphosphate glucuronosyltransferases (UDPGT) into two compounds; morphine-6-glucuronide (M6G, a potent analgesic and respiratory depressant) and morphine-3-glucuronide (M3G, which antagonizes the action of morphine and M6G). Morphine and its metabolites are excreted via the kidneys so it should be used cautiously in the presence of renal disease/failure. Morphine has poor oral bioavailability (20–30%), has histamine release associated with its use, and may cause vasodilatation with hypotension in hypovolemic patients. Morphine is a very hydrophilic compound and does not cross the blood–brain barrier very well. The clearance and elimination half-life of morphine are shorter in children than adults, and a smaller dosing interval may be necessary to achieve adequate pain control (Hain et al. 1999; Hunt et al. 1999). Immediate-release morphine should be prescribed with a dosing frequency of every 2–4 h.

Hydromorphone is a morphine analog with similar pharmacokinetic and pharmacodynamic properties but is 5–7.5 times more potent than morphine with minimal active metabolites so it may be useful in patients with renal disease. Systematic reviews in adult patients have not demonstrated any differences between morphine and hydromorphone with respect to analgesic efficacy, adverse effects, or patient preference (Quigley and Wiffen 2003). Fentanyl is a highly lipid-soluble synthetic opioid with a rapid onset of action. It is 50–100 times more potent than morphine and has no active metabolites. Tolerance and dependence may occur rapidly, and fentanyl is available as a transdermal patch for patients.
with chronic pain. The transdermal fentanyl is absorbed across the skin and is stored in the upper layers of the skin providing a secondary reservoir of agent which contributes to the prolonged action of the drug even after removal of the patch. Transdermal fentanyl should only be used for opioid-tolerant individuals for chronic pain. The fentanyl patch is available in the following sizes: 12.5 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, and 100 mcg/h. The patches cannot be physically cut into smaller pieces so must be placed intact on the skin (Finkel et al. 2005; Zernikow et al. 2007).

Fentanyl is also available as a buccal transmucosal oralet (Actiq®) for use for procedural pain or as an agent for breakthrough pain. The fentanyl is placed in a candy matrix such that buccal absorption occurs with subsequent rapid systemic absorption of agent (10–20 min). The typical dose of transmucosal fentanyl is 10–15 mcg/kg and will last for approximately 2 h. The major adverse effects of transmucosal fentanyl are nausea and vomiting with a prevalence of 20–33%. A new, rapidly dissolving buccal tablet, Fentora®, is also available for the treatment of breakthrough pain; the tablets are available in the following doses: 100, 200, 400, 600, and 800 mcg), and approximately 50% of the total dose is absorbed transmucosally and 50% is swallowed with slow absorption via the GI tract (Messina et al. 2008; Weinstein et al. 2009). There is only anecdotal use of this agent in children.

Methadone is a unique synthetic, long-acting opioid agonist that is a racemic mixture of two isomers. The drug is a μ-receptor opioid agonist with some activity also at the δ and κ receptors; it is also a N-methyl-d-aspartate (NMDA) receptor antagonist. The NMDA receptor is associated with central sensitization, wind-up phenomenon, opioid-induced hyperalgesia, and the development of tolerance; thus, methadone may prevent these detrimental effects via antagonism of the NMDA receptor (Ebert et al. 1998; Gorman et al. 1997). The L-isomer of methadone inhibits serotonin and norepinephrine reuptake as well. Methadone may be administered by the oral, rectal, intravenous, or nasal route. The drug is lipophilic with high oral bioavailability (80–90%) and is slowly metabolized in the liver. The metabolites of methadone are not pharmacologically active. This agent has a long and unpredictable elimination half-life ranging from 12 to 200 h. A single dose of methadone may provide 12–36 h of analgesia (Gourlay et al. 1984). The analgesic efficacy is much shorter than the elimination half-life. The potency of methadone is roughly equal for opioid-naïve patients; however, the potency of methadone is 4–20 times that of oral morphine with opioid-tolerant patients. The conversion of oral morphine to methadone is dose-dependent and is as follows (Houlahan et al. 2006):

<table>
<thead>
<tr>
<th>Oral morphine (mg/24 h)</th>
<th>Oral morphine/oral methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>4:1</td>
</tr>
<tr>
<td>101–300 mg</td>
<td>8:1</td>
</tr>
<tr>
<td>301–600</td>
<td>10:1</td>
</tr>
<tr>
<td>601–1,000</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1,000</td>
<td>20:1</td>
</tr>
</tbody>
</table>

The practitioner must use caution when switching from another opioid to methadone. After using the table to calculate equianalgesic dose of methadone, the calculated dose should be decreased by 50%, because of methadone inhibition of NMDA receptor. The agent is usually given as BID or TID dosing. Methadone is also a potent blocker of the delayed rectifier potassium ion channel with can result in prolongation of the QT interval, torsade de pointes, and ventricular tachycardia in susceptible individuals (Andrews et al. 2009). The effect of methadone on the QT interval may be enhanced by hypokalemia or the concomitant use of CYP 3A4 inhibitors such as fluoxetine, Valproate, or clarithromycin (Andrews et al. 2009; Ehret et al. 2006). Some practitioners are advocating routine ECG prior to initiation of therapy with methadone and regular ECG assessment during therapy.

Adverse effects due to opioids are not uncommon, and constipation is a predictable side effect with prolonged use. It occurs in virtually all cases, so a prescription to treat constipation should be administered as soon as an opioid is started. Sedation with opioid use is common and can significantly impact the child and the family’s quality of life. If sedation doesn’t dissipate after a few days, add an adjuvant drug and decrease the
opioid dose, give the patient a stimulant such as methylphenidate or dextroamphetamine, or consider switching to a different opioid. Nausea and/or vomiting may occur with opioid use and can be treated by opioid rotation, the use of selective 5-HT3 receptor antagonists such as ondansetron, the addition of a bowel stimulant such as metoclopramide (Watcha and White 1992), or the use of an ultra-low dose naloxone infusion (0.25–1 mcg/kg/h) in patients with IV access (Maxwell et al. 2005). Pruritis is treated by opioid rotation, use of adjuvants to decrease opioid dose, or antipruritics such as naloxone (Maxwell et al. 2005), nalbuphine (Kendrick et al. 1996), or diphenhydramine. Respiratory depression is another potential side effect of opioids and is often cited by practitioners as a reason for not prescribing opioid analgesics for pain. However, an opioid-induced respiratory depression is less common than many practitioners believe and can largely be avoided with standard dosage titration and frequent monitoring in at-risk patients. Respiratory depression, if it does occur, is treatable with an opioid antagonist, stimulation, and bag/mask ventilation if necessary. Unless the patient is experiencing severe respiratory depression with hypoxia, small doses of naloxone (1–2 mcg/kg/dose) given every few minutes will often improve sedation without reversing the analgesic effects of the opioid. The patient will usually develop tolerance to the analgesic efficacy and the adverse effects of opioids with prolonged use with the exception of constipation. Frequent monitoring for efficacy and the development of adverse effects is needed, and, if the patient is developing tolerance to the medication, then the provider should consider opioid rotation. Switching to another agent will take advantage of the phenomenon of incomplete cross-tolerance in which lower doses vis-à-vis the recommended equianalgesic dose can be used with analgesic efficacy.

Co-analgesics/Adjuvant Analgesics
These are a diverse group of medications that may enhance the effects of nonopioid or opioid analgesics, have independent analgesic activity in certain pain syndromes or conditions, or counteract the side effects of analgesics. They represent multiple drug classes including the following: antidepressants, anticonvulsants, local anesthetics, corticosteroids, antispasmodic agents, benzodiazepines, alpha-2 adrenergic agents, NMDA-receptor antagonists, stimulants, skeletal muscle relaxants, bisphosphonates, calcitonin, radionuclotides, and cannabinoids. For many of these agents, their primary indication is for conditions other than pain. These adjuvant agents are especially useful for the treatment of neuropathic pain which may be a common problem in many chronic pain conditions; in fact, approximately 40–50% of adults with cancer have neuropathic pain, usually in combination with nociceptive pain (Manfredi et al. 2003). These medications are very commonly added to opioids to improve pain relief, manage refractory pain, or allow lower doses of opioids to reduce side effects. As with any medications, the use of these agents to treat chronic pain involves the weighing of potential benefit of the therapy compared to the risks and adverse effects of the therapy. Many of these medications may be safely used in children if the dose is adjusted for the weight of the patient; however, most of these medications do not have FDA approval for use in children. The efficacy and safety of these agents may not have been adequately evaluated in well-designed clinical trials in children (Table 20.4).

Antidepressants
Antidepressants are useful agents in the management of chronic pain (Saarto and Wiffen 2007). There are a variety of potential mechanisms of action for these drugs including the following: monoamine modulation, interactions with opioids, affecting the descending inhibitory pathways for pain expression, and ion-channel blocking. These agents block the presynaptic reuptake of serotonin and/or norepinephrine in the CNS, stabilize neuronal membranes through inhibition of sodium channels, and inhibit neuronal hyperexcitability through NMDA antagonist-like effects (Sindrup et al. 2005). They also provide improved pain control and well-being by their beneficial treatment of depressive symptoms and insomnia that often occur concomitantly with chronic pain.
<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Usual effective adult dose</th>
<th>Pediatric dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants (TCAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10–25 mg qhs</td>
<td>50–150 mg qhs</td>
<td>Initial dose 0.2–0.3 mg/kg qhs or BID Titrate: 0.25 mg/kg (10–25 mg) every 5–7 days Maintenance: 0.2–3 mg/kg (10–150 mg)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10–25 mg qhs</td>
<td>50–150 mg qhs</td>
<td>As above for amitriptyline. Fewer anticholinergic side effects and less sedating than amitriptyline, drug levels available, agent available as elixir (10 mg/5 mL), common first line Max dose is 150 mg for adults or 3 mg/kg/day in children. Agent for neuropathic pain.</td>
</tr>
<tr>
<td>Desipramine</td>
<td>10–25 mg qhs</td>
<td>50–150 mg qhs</td>
<td>Safety</td>
</tr>
<tr>
<td><strong>Serotonin norepinephrine reuptake inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg qd</td>
<td>150–225 mg qd</td>
<td>Safety and efficacy not determined for pediatric patients. 1–2 mg/kg as divided doses</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20 mg qd</td>
<td>60 mg qd</td>
<td>Safety and efficacy not determined for pediatric patients.</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10–20 mg qd</td>
<td>20–40 mg qd</td>
<td>Safety and efficacy not determined for pediatric patients.</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10–20 mg qd</td>
<td>20–40 mg qd</td>
<td>Safety and efficacy not determined for pediatric patients.</td>
</tr>
<tr>
<td><strong>Antiepileptic drugs (AEDs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100–300 mg qhs</td>
<td>300–1,200 mg TID</td>
<td>Initial dose 2 mg/kg/day. Titrate to 5–30 mg/kg/day as TID dosing</td>
</tr>
</tbody>
</table>

(continued)
Table 20.4 (continued)

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Usual effective adult</th>
<th>Pediatric dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregabalin</strong></td>
<td>75–150 mg qd</td>
<td>300–600 mg daily as BID dosing</td>
<td>Not FDA-approved for use in children. Weight gain occurs with some patients. Faster titration than gabapentin with faster pain relief.</td>
</tr>
<tr>
<td><strong>Sodium-channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100–200 mg qd</td>
<td>300–800 mg qd</td>
<td>Initial: 10 mg/kg/day as BID/TID dosing. Titrator by 100 mg/day at weekly intervals as needed. Do not exceed 800 mg or 30 mg/kg/day. Many drug–drug interactions. Monitor hematological function (CBC) prior to and during therapy. Side effects common and include hematologic, CNS, and cardiac. Oral suspension (100 mg/5 mL) is available. Drug levels available.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25 mg qd</td>
<td>100–200 mg BID</td>
<td>Seizure dosing: 0.15 mg/kg/day (rounded to nearest whole tablet) in 1–2 divided doses for 2 weeks, and then 0.3 mg/kg/day (rounded to nearest whole tablet) in 1–2 divided doses. Increase to usual maintenance dose of 1–5 mg/kg/day (max 200 mg). Adverse effects include somnolence, dizziness, and ataxia. Rarely associated with Stevens-Johnson syndrome.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25 mg qd</td>
<td>100–200 mg BID</td>
<td>1–3 mg/kg/day qhs for 1 week, then increase dose by 1–3 mg/kg/day (as BID dosing) at 1–2 week intervals to usual 25–400 mg/day May cause hyperchloremic non ion gap metabolic acidosis so periodic measurement of sodium bicarb levels during Rx is recommended.</td>
</tr>
<tr>
<td>Valproate</td>
<td>250 mg TID</td>
<td>500–1,000 mg TID</td>
<td>Initial dose of 10–15 mg/kg/day. Titrator to maximum of 30–60 mg/kg/day as TID dosing. Approved as migraine prophylaxis in adults but not for children.</td>
</tr>
<tr>
<td><strong>a₂-adrenergic agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg po qd</td>
<td>Variable</td>
<td>2–5 μg/kg/day po as TID/QID dosing or as 0.1 mg transdermal patch. Epidural dosing is 1–2 μg/kg loading dose with continuous epidural infusion of 0.02–0.1 μg/kg/h to maximum epidural dose of 0.2 μg/kg/h. Side effects include bradycardia, hypotension, and sedation which limit clinical utility.</td>
</tr>
</tbody>
</table>
### NMDA-receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Adult Dose</th>
<th>Pediatric Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>0.2–0.5 mg/kg IV</td>
<td>0.2–0.5 mg/kg IV loading dose over 30 min f/b continuous infusion between 0.14 and 0.5 mg/kg/h</td>
<td>Not FDA-approved for use in children &lt;16 years of age. Elevates pain threshold and is used as co-analgesic with opioids. Useful for neuropathic pain as well as attenuation of opioid-induced hyperalgesia. Oral ketamine has poor bioavailability (20%).</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>15–20 mg TID</td>
<td>Unknown</td>
<td>Not commonly used as analgesic.</td>
</tr>
<tr>
<td>Memantine</td>
<td>5 mg qd</td>
<td>10 mg BID</td>
<td>Safety and efficacy not established for children.</td>
</tr>
</tbody>
</table>

### Membrane stabilizers/local anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Adult Dose</th>
<th>Pediatric Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine IV</td>
<td>2 mg/kg over 2 min</td>
<td>2–5 mg/kg</td>
<td>Measure plasma level every 8–12 h and maintain 2–5 µg/mL.</td>
</tr>
<tr>
<td>Topical 5% lidocaine patch</td>
<td>1 patch 12 h/24 h</td>
<td>1–3 patches 12 h/24 h</td>
<td>FDA-approved for PHN and useful for many neuropathic pain syndromes in adults. Cut patch as needed without loss of agent and can be used over multiple areas topically. Minimal systemic effects and plasma concentrations.</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>150 mg qd</td>
<td>100–300 mg TID</td>
<td>Frequent side effects limit the utility of this agent and include nausea/vomiting, sedation, ataxia. IV lidocaine trial may predict success of this agent. Drug levels available.</td>
</tr>
</tbody>
</table>

### Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Adult Dose</th>
<th>Pediatric Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>4 mg BID</td>
<td>Variable</td>
<td>Indication for use is rapidly escalating pain with significant functional impairment. Side effects include weight gain, edema, dyspepsia, osteoporosis, Cushing’s syndrome, psychosis.</td>
</tr>
</tbody>
</table>

*BID* twice a day, *TID* three times a day, *QID* four times a day, *PHN* postherpetic neuralgia
Antidepressants have analgesic effects that are independent of their antidepressant effects.

Several systematic reviews and meta-analyses have determined that tricyclic antidepressants (TCAs) are effective for many neuropathic pain syndromes [postherpetic neuralgia (PHN), painful peripheral diabetic neuropathy, central post-stroke pain, and trigeminal neuralgia]; however, they do not appear to be useful in the treatment of HIV-related neuropathies (Saarto and Wiffen 2007; Sindrup et al. 2005). TCAs are inexpensive, effective, and usually require once-daily dosing (potentially improving compliance with treatment); thus, they are often first-line medications for the treatment of neuropathic pain. Secondary amine TCAs (nortriptyline and desipramine) are better tolerated than the tertiary amines (amitriptyline/imipramine) and are equally efficacious. Nortriptyline has less anticholinergic side effects than amitriptyline, and is a common first-line agent used in the treatment of neuropathic pain. Nortriptyline is available in liquid form (10 mg/5 ml solution) for use in young children or given via gastrostomy tube in patients unable to take medications orally. Common side effects include sedation, dry mouth, orthostatic hypotension, constipation, urinary retention, and tachycardia (Knotkova and Pappagallo 2007; Kong and Irwin 2009).

A small number of patients who have received TCAs have had sudden death attributed to dysrhythmia (Amitai and Frischer 2006). It is unknown whether these children had a preexisting conduction disturbance, and these drugs have been used safely in children for decades. A baseline ECG should be obtained to rule out rhythm disturbances prior to starting a TCA and also when escalated to a full antidepressant dose range (Dworkin et al. 2007). These drugs should be used with extreme caution in patients with preexisting rhythm disturbances or cardiomyopathy. There is no established correlation between plasma concentration of TCAs and analgesic efficacy; therefore, routine measurement of plasma drug levels is useful only to determine patient compliance, optimization of dose before aborting a therapeutic trial, or to identify patients that need dosing modification based on metabolism of the drug (i.e., those patients who may need b.i.d. dosing). If the drug needs to be discontinued for any reason, the dosing should be tapered over 1–2 weeks to avoid irritability and agitation.

Other antidepressants have been used for neuropathic pain but have not provided similar efficacy compared to the tricyclic antidepressants. Serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine (Cymbalta®) and venlafaxine (Effexor®) do not possess the anticholinergic and antihistaminergic effects of the TCAs. Venlafaxine has been demonstrated to modulate allodynia and hyperalgesia in human models and to relieve neuropathic pain associated with breast cancer (Grothe et al. 2004; Rowbotham et al. 2004). Duloxetine has been recently approved by the FDA for the treatment of pain associated with diabetic neuropathy (Fishbain et al. 2006; Wernicke et al. 2006; Wernicke et al. 2007). In a study by Meighen, duloxetine was shown to be effective in the treatment of chronic pain and co-morbid depressive disorders in two adolescents (Meighen 2007). The selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and fluoxetine are relatively ineffective as analgesics but are helpful with associated depression, sleep disturbance, and anxiety (Max et al. 1992).

**Anticonvulsant Drugs (AEDs)**

Anticonvulsant or antiepileptic agents are a diverse group of agents with varied mechanisms of action to treat pain. These drugs are often first-line agents for the treatment of neuropathic pain and other painful chronic or recurrent pain conditions such as migraine headaches. The primary mechanism of action of these agents is to reduce the ectopic, spontaneous firing of cortical neurons which cause seizures leading to a dampening or attenuation of the neuronal excitability. It is presumed that these agents also reduce the ectopic, spontaneous firing of sensory neurons in the spinal dorsal horn or dorsal root ganglion (DRG) leading to the up-regulation of Na+ and Ca++ after nerve injury which may lead to the onset of neuropathic pain and sensitization.

The calcium-channel α-2-δ ligands [gabapentin (Neurontin®)/pregabalin (Lyrica®)]
have established efficacy in the treatment of neuropathic pain and are common first-line agents in adults, and gabapentin is commonly used in pediatric pain management (Butkovic et al. 2006; Dayioglu et al. 2008). There are few studies of the use of pregabalin in pediatric patients for pain management (Vondracek et al. 2009). Gabapentin and pregabalin do not act on the γ-aminobutyric acid (GABA) receptors or sodium channels. These agents modulate the cellular calcium influx into nociceptive neurons by binding to the voltage-gated calcium channel (especially the α2δ subunit) resulting in decreased release of glutamine, norepinephrine, and substance P. Calcium-channel alpha-2-delta ligands such as gabapentin and pregabalin have been shown to be useful for the treatment of phantom limb pain, neuropathic cancer pain, and peripheral neuropathies. There are a few case reports describing the utility of gabapentin and pregabalin for the treatment of neuropathic pain in children (Butkovic et al. 2006; Carrazana and Mikoshiba 2003; Dayioglu et al. 2008; Lauder and White 2005; Vondracek et al. 2009).

Gabapentin has become the first-line drug for the treatment of postherpetic neuralgia (PHN), painful diabetic peripheral neuropathy, phantom limb pain, Guillian-Barré syndrome, neuropathic cancer pain, and chronic spinal cord injury. The number needed to treat (NNT) for neuropathic pain is 2.5. This agent has a less favorable side effect profile and requires monitoring of hematological function (CBC prior to therapy and every 3–6 months while receiving the agent) so clinicians are not using this agent as a first-line therapy very often. Adult dosing is 100–200 mg daily with titration to 300–800 mg BID. The recommended pediatric dosing is 10 mg/kg/day as BID or TID dosing initially with titration by 100 mg weekly as needed [max dose 30 mg/kg/day]. A suspension of 100 mg/5 cc is available for use. Common adverse effects are hematologic (aplastic anemia, agranulocytosis), cardiovascular (CHF, syncope, dysrhythmias), CNS (sedation, dizziness, fatigue, slurred speech, ataxia), and hepatitis (Lussier et al. 2004). Oxcarbazepine (Trileptal®) is the keto-analog of carbamazepine, and its mechanism of action is to

Pregabalin is the first FDA-approved medication for the treatment of fibromyalgia and has strong evidence of analgesic efficacy. The efficacy of pregabalin has been demonstrated in multiple randomized controlled trials in adults for the treatment of various neuropathic pain syndromes such as PHN, painful peripheral diabetic neuropathy, mixed neuropathic pain, and spinal cord injury pain. As with many agents, pregabalin is not FDA-approved for use in children. One open-label study in 30 pediatric oncology patients with neuropathic pain demonstrated a significant improvement in symptoms with very infrequent adverse effects (Vondracek et al. 2009).
inhibit voltage-sensitive sodium channels as well as high-voltage-activated calcium channels. Recent open-label studies have shown potential efficacy in the treatment of painful peripheral diabetic neuropathy (Carrazana and Mikoshiba 2003), and a case report in the literature showed improvement in pain control in a child with complex regional pain syndrome (CRPS) refractory to other treatments (Lalwani et al. 2005). At this time, without evidence of efficacy and safety, routine use of this agent is not recommended.

Several newer anticonvulsant drugs (lamotrigine, topiramate, zonisamide, and levetiracetam) have been studied for efficacy in a variety of pain conditions in adults, especially primary headache management. Despite the broad use of these agents for the treatment of neuropathic pain, no trials have been conducted in the pediatric population. Thus, at this time, there is inadequate evidence to recommend the use of these agents for the treatment of neuropathic pain in children. Topiramate and valproate are approved for migraine prophylaxis in adults; however, no AEDs have been approved for migraine prophylaxis in children. Open-label studies and chart reviews have supported the use of valproate for this purpose, and topiramate and levetiracetam have been evaluated for pediatric migraine prophylaxis with promising results. However, currently no AED is formally recommended for migraine prophylaxis in children and adolescents.

**α₂ - Adrenergic Agents**

The α₂-adrenergic agents, clonidine, tizanidine, and dexmedetomidine, are agents used for analgesia and sedation; the mechanism of action of these agents is by modulation of norepinephrine by the α₂ receptor subtype in the spinal cord leading to analgesia. Clonidine is a well-known agent that has been used clinically to treat neuropathic pain associated with diabetes. Clonidine can be administered via the oral, transdermal, or epidural route. Clonidine is known to potentiate the analgesic effect of opioids. Clonidine increases the release of acetylcholine at the spinal dorsal horn and activates spinal acetylcholine receptors enhancing the sensory and motor block of C fibers and A-δ fibers by local anesthetics. The epidural administration of clonidine results in a peak analgesic effect within 60 min and a duration of effect as long as 6 h. Most pediatric studies of clonidine have focused on the epidural use in post-operative pain management. Extrapolation of adult dosing has led to a recommended loading dose of 1–2 mcg/kg with a continuous epidural infusion of 0.02–0.1 mcg/kg/h titrating to a maximum dose of 0.2 mcg/kg/h.

Transdermal clonidine has been demonstrated to be useful for some patients with painful peripheral diabetic neuropathy, and oral clonidine has been effective in the treatment of postherpetic neuralgia in a clinical trial in adults (Byas-Smith et al. 1995). Clonidine is given as 2–5 mcg/kg/day orally as every 6–8 h dosing (TID/QID) or as a 0.1 mg transdermal patch. The analgesic benefits of clonidine are only supported with limited data, and the side effect profile (bradycardia, hypotension, and sedation) limits its usefulness in some situations. Thus, it is not a first-line agent for chronic pain. Tizanidine is principally used for the management of spasticity and is reported to be useful for the treatment of some neuropathic pain disorders, chronic daily headache, migraine prophylaxis, and chronic back pain in adults (Semenchuk and Sherman 2000).

**NMDA-Receptor Antagonists**

Central and peripheral NMDA receptors may have a role in the management of hyperalgesia and chronic pain. NMDA receptors in the spinal cord are activated by repeated stimuli in nociceptive afferent nerves leading to central sensitization of dorsal horn cells resulting in perpetuation of pain sensation and reduced opioid sensitivity. NMDA antagonists may reduce pain by two mechanisms: reduction in central sensitization and reduction in opioid tolerance. The NMDA receptor is associated with the development of tolerance and hyperalgesia from opioids so NMDA receptor antagonists have been used to attenuate or reverse these effects. The N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine, methadone, dextromethorphan, memantine, and amantadine) would theoretically have utility for the management of hyperalgesic neuropathic pain that is poorly responsive to opioids.
Ketamine is an NMDA-receptor antagonist that is used as an analgesic adjuvant in poorly controlled pain (Finkel et al. 2007). Ketamine is a mixture of two enantiomers, and the S (+) enantiomer has 4X the potency of the R (−) enantiomer. It is a noncompetitive antagonist of the NMDA receptor. Ketamine is also an opioid-receptor agonist and a serotonin/norepinephrine reuptake inhibitor. It elevates the pain threshold and is used as a co-analgesic with opioids. Subtherapeutic dosing of 0.25–0.5 mg/kg loading dose over 30 min followed by a continuous infusion between 0.14 and 0.5 mg/kg/h may be useful for neuropathic pain as well as attenuation of opioid-induced hyperalgesia (Tsui et al. 2004). NMDA-receptor blocking agents such as ketamine have been shown to decrease opioid requirements and improve pain control in a few case reports (Finkel et al. 2007; Grande et al. 2008).

The onset of action of ketamine is within 1–3 min of dosing due to the drug’s lipophilicity and small size. Ketamine likely provides an additive analgesic effect as well as reversing opioid tolerance. Ketamine is metabolized to norketamine which has 1/3rd of the potency of the parent compound. Ketamine has a short elimination half-life of approximately 3 h so steady-state would be achieved in 12–15 h from the initial administration of the agent. Oral ketamine has poor oral bioavailability (20%) with 80% of the dose metabolized to norketamine at the first-pass. Adverse effects from ketamine include hypertension, tachycardia, increased muscle tone, increased ICP, psychomimetic effects (alterations in body image and mood, floating sensations, vivid dreams, hallucinations, delirium, and drowsiness). Rarely, respiratory depression may occur with use of ketamine.

Other NMDA-antagonists such as dextromethorphan and memantine have not been commonly used for children with neuropathic pain. Memantine is a relatively newer NMDA-antagonist that is FDA approved for the treatment of dementia in moderate to severe Alzheimer disease. Studies to date with this drug for neuropathic pain has led to equivocal results (Rogers et al. 2009) with some investigators reporting successful treatment with CRPS (Sinis et al. 2007) while others have reported no analgesic efficacy with chronic phantom limb pain (Wiech et al. 2004). One study suggested that early use of memantine after surgical amputation was effective in reducing phantom limb pain (Schley et al. 2007). There are no studies to support the use of memantine for the treatment of chronic pain in children although the drug has been shown to be safely used in pediatric patients for the treatment of autism spectrum disorders (Chez et al. 2007). Studies of the use of dextromethorphan as an analgesic in children have produced mixed results (Dawson et al. 2001; Rose et al. 1999), and it is not commonly used as an analgesic in children.

Membrane Stabilizers/Local Anesthetics
Both animal and human studies demonstrate that injured nerves develop abnormal, spontaneously active sodium channels at the site of nerve injury, along the damaged nerve, and at the dorsal root ganglion of the injured nerve. Local anesthetics will suppress the spontaneous firing of these aberrant sodium channels without affecting normal nerve conduction or cardiac impulse conduction. Membrane-stabilizing agents (lidocaine, mexiletine) are potentially useful in the treatment of neuropathic pain (Ferrini 2000; Kastrup et al. 1987; Tremont-Lukats et al. 2006). Lidocaine is a local anesthetic that is a nonselective sodium channel blocker which may be useful in the treatment of neuropathic pain; however, it is not a first-line agent in the treatment of chronic, neuropathic pain. Small studies have established that lidocaine is effective in the treatment of postherpetic neuralgia and painful peripheral diabetic neuropathy; it was shown to be more effective than placebo in the treatment of neuropathic pain and is generally well tolerated. There is conflicting data as to the effectiveness of lidocaine for cancer-related pain. A therapeutic response to lidocaine may predict a similar response to mexiletine, an oral congener of lidocaine that is an antiarrhythmic agent. Multiple dosing regimens have been reported for use, but the typical loading dose is 1–5 mg/kg IV administered over 15–60 min depending on the total dose. The time to analgesic effect is between 1 and 45 min.
If the patient has a therapeutic response to the lidocaine test, then the patient may be given a continuous infusion over hours or days if needed (e.g., palliative care).

Lidocaine is rapidly and extensively metabolized in the liver and is excreted by the kidneys. Serum lidocaine levels should be followed at steady state (elimination half-life is approximately 100 min so 3–5 half-lives would be 5–8 h; the target serum plasma level is 2–5 mg/mL. Adverse effects are related to dose of agent and can occur when serum levels are >5 mg/mL. Myoclonus will occur with serum levels at 8 mg/mL, seizures at >10 mg/mL, and cardiovascular collapse at levels >25 mg/mL.

The use of lidocaine infusion of opioid-refractory pain was reported by Sharma et al. In this phase II randomized, placebo-controlled crossover study of refractory cancer pain in 50 patients, an improvement in pain relief and decrease in analgesic use was seen with a 60-min infusion of lidocaine. The effect of treatment persisted for an average of 9 days and with minimal tolerable side effects of therapy (Sharma et al. 2009). In a study by Schwartzman et al. of 49 patients with CRPS who were given a 5-day IV infusion of lidocaine titrated to 5 mL/L, the majority of patients reported a significant reduction in pain and signs/symptoms of CRPS that persisted for approximately 3 months (Schwartzman et al. 2009). There are a few case reports of the use of lidocaine infusion for neuropathic pain in children. Massey et al. reported a successful treatment of a 5-year-old child with terminal cancer pain using a continuous lidocaine IV infusion between 35 and 50 mcg/kg/min over 4 days with excellent pain relief and no side effects (Massey et al. 2002). There is another case report of an 11-year old with erythromelalgia with numerous pain episodes daily (20–30/day), who was successfully treated with IV lidocaine infusion that was transitioned to oral mexiletine with significant decrease in the intensity and frequency of the pain episodes and greatly improved function (Nathan et al. 2005). Mexiletine was originally used as an oral cardiac antiarrhythmic analog of lidocaine, and it has been used to treat neuropathic pain which is responsive to lidocaine infusion. Mexiletine has been used in doses as high as 10 mg/kg daily to treat diabetic neuropathy as well as pain associated with peripheral nerve injuries. There is no pharmacokinetic or pharmacologic difference in the absorption or metabolism of mexiletine between adults and children. This agent is associated with frequent side effects which limit its utility as an analgesic for chronic pain; these adverse effects include nausea/vomiting, sedation, confusion, difficulty concentrating, diplopia, and ataxia.

More commonly, the 5% transdermal lidocaine patch is used for neuropathic pain. The topical lidocaine 5% patch (Lidoderm®) is FDA-approved for the treatment of PHN and is associated with a reduction in pain in a variety of neuropathic pain syndromes in adults, including painful peripheral diabetic neuropathy, CRPS, post-mastectomy pain, and HIV-associated neuropathy. It is applied for 12 h/day with a maximum use of three patches at one time in the adult patient. The patch may be cut to size without loss of agent and used over multiple areas topically. There are minimal systemic effects and plasma concentrations (1/10 for cardiac effects and 1/32 for toxicity). In a study of five adolescents with chronic neuropathic pain, the use of 5% lidocaine patches were associated with improved analgesia in 80% of patients (Nayak and Cunliffe 2008).

Other Adjuvant Agents
Corticosteroids (e.g., dexamethasone or prednisone) are effective for the treatment of inflammatory neuropathic pain associated with peripheral nerve injury, pain associated with bone metastasis, pain associated with bowel obstruction, and headache pain associated with increased intracranial pressure (Shih and Jackson 2007). The analgesic effect of corticosteroids has been described for a broad range of doses. Indication for the use of corticosteroids is usually rapidly escalating pain with significant functional impairment. Common adverse effects of corticosteroids when used chronically or at high doses include weight gain, edema, dyspepsia, osteoporosis, Cushing’s syndrome, psychosis, and rarely GI bleeding (Knotkova and Pappagallo 2007).
Bisphosphonate therapy is useful for pain related to bone metastases and has been used for the treatment of pain due to complex regional pain syndrome (CRPS) (Cortet et al. 1997; Varenna et al. 2000). In a study by Simm et al., bisphosphonates were used to treat five patients with chronic recurrent multifocal osteomyelitis with an 80% response rate (Simm et al. 2008). Pamidronate was used to treat intractable, chronic neuropathic pain in two adolescents with no evidence of improvement in pain or function (Brown et al. 2005). Thus, there are a few conflicting reports concerning the potential efficacy of bisphosphonates for children with chronic pain. Adverse effects from use of bisphosphonates include electrolyte abnormalities, GI symptoms (dyspepsia, reflux, nausea, and abdominal pain), and osteonecrosis of the jaw.

Cannabinoids have been shown to have analgesic properties in animal models and clinical observations. The mechanism of action for analgesia is via a peripheral anti-inflammatory action (Knotkova and Pappagallo 2007). Cannabinoids have been reported to be helpful in the management of neuropathic pain associated with multiple sclerosis (Rog et al. 2005). Good evidence for the efficacy of cannabinoids is lacking; however, there is a report of the effective use of the synthetic cannabinoid CT-3 (1',1'-dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid) for the treatment of chronic neuropathic pain (Karst et al. 2003). In a case report by Rudich et al., dronabinol (Marinol®) was reported to be effective in the treatment of chronic intractable neuropathic pain in two adolescents (Rudich et al. 2003). Adverse effects include cognitive impairment, psychosis, and sedation.

**FDA and Pediatric Drugs**

Although only 15% of drugs listed in the *Physicians' Desk Reference* have labeled indications for children, it is common practice that providers prescribe medications off-label for children. These off-label prescriptions include not only dose adjustments (often by weight or body surface area) via the labeled route for adult patients, but also use for illness or conditions not included in labeling, and use via routes of administration not included in the product label (e.g., nasal fentanyl or midazolam, and clonidine for regional nerve blockade). A recent review of the literature suggests that the pharmacokinetics and pharmacodynamics of medications in neonates and children may not be well predicted by adult values, and that children may likely require significant adjustments in dose or interval for optimal efficacy and to minimize side effects. The United States Congress has enacted several laws intended to directly promote drug development for children, and these measures have increased the amount of information on the safe and efficacious use of drugs for children. The Food and Drug Administration Modernization Act (FDAMA) was passed in 1997 (Food And Drug Administration 1997), and offered pharmaceutical companies a 6-month period of marketing exclusivity if they performed studies in pediatric patients in response to a written request issued by the FDA. Marketing exclusivity incentives were attached to a period of existing patent protection or exclusivity and have been effective in prompting industry to conduct needed pediatric trials for drugs with existing patent protection or exclusivity. However, this program did not provide any incentivization for the study of off-patent, mostly generic, drugs due to the costs and risks of performing pediatric medication trials. Often by the time a pediatric trial has been conceived or performed, the drug is nearing its patent expiration and the trials cannot be completed in time to provide an adequate return on investment for the sponsor. With the common practice of off-label use and the paucity of available data concerning pediatric patients, the US Congress passed the Best Pharmaceuticals for Children Act (BPCA) in 2002. This legislation empowered the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) to fund studies of generic pharmaceuticals in children in which the sponsors would not support the study because of costs, risks, and lack of economic incentives. The Pediatric Research Equity Act (PREA) in 2003 codified the authority of the FDA to require pediatric studies of certain drugs and biologic agents (108th Congress 2009).
With the passage of these three laws, there has been a greater emphasis on the study of medications in the pediatric population in order to determine effectiveness and safety of therapeutic agents. Trials of pharmaceuticals with potential use for children have recently begun to evaluate agents in common use.

**Computerized Provider Order Entry and Pediatric Patients**

Medication errors are the most common type of medical error with significant potential for adverse events (ADE) (Bates et al. 1995b; Institute of Medicine and Committee on Quality Health Care in America 2000). According to the Committee on Quality Health Care in America, a medication error is any preventable event that occurs in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present (Bates et al. 1995b; Institute of Medicine and Committee on Quality Health Care in America 2000). While human mistakes play an important role, over half of medication errors are preventable (Kelly 2001) and occur as a result of system flaws. Medication errors may occur at any step in the process but provider errors are common.

Most safety research has centered on medication errors and their prevention in adult patients. For adults, the reported incidence of medication errors is 1 in 20 written orders (Bates et al. 1995a). In a 2005 study in adult primary care practices, the medication error rate was 7.6% in a center with a basic computerized prescribing system which lacked dose and frequency checking. (Gandhi et al. 2005) In pediatrics, the error rate has been reported to be as high as one in six orders for inpatients with 31% associated with harm or death (Marino et al. 2000). Children are at a higher risk for ADEs, estimated as nearly triple that of adults.

In a study from my institution examining prescribing medication error rates for analgesics in children being discharged from the hospital, we found the process to be error-prone with approximately 3% of prescriptions with the potential for causing an adverse drug event (ADE) (Lee et al. 2009). Because of the complexity of medication dosing in the pediatric patient, pediatric patients are at higher risk than adults for dosing error and errors involving controlled substances (or narcotics) are the most dangerous. We developed a web-based controlled substance prescription writer that included weight-based dosing logic and alerts. We implemented the web-based program and evaluated the error reduction, behavior modifications, and attitudes toward the use of the application. We found that the web-based controlled substance prescription writer prevented analgesic medication errors by alerting users that their doses exceeded hard limits for weight-based dosing. The use of alerts changed prescriber behavior and prevented the potential for future medication errors as demonstrated by the increased likelihood of abandoned prescription attempts with alerts (Zimmer et al. 2008).

Even with limited data, it is empirically evident that pediatric patients are at higher risk for error due to several key factors. Most drug doses in pediatrics are weight-or body surface area-based and may be modified by other factors including age (Wong et al. 2004). Weight-based medication orders have a dosing error rate of 10.3% compared to 5.9% for non-weight-based drugs (Herout and Erstad 2004). A substantial proportion of providers make mistakes while calculating drug doses, (Rowe et al. 1998) often by an order of magnitude. Process factors, including the need for individualized dilution of stock medications and fluids, place children at increased risk for dispensing errors. Pharmacokinetic factors, including age based variability in absorption, metabolism, and excretion of drugs as compared with adults, expose special vulnerabilities to the adverse effects of overdosing (Lehmann and Kim 2005; Kanter et al. 2004). Given the prevalence of prescribing errors, there is a need for systematic changes to reduce the likelihood of errors. Computerized provider order entry (CPOE) with clinical decision support (CDS) has been shown to be one of the most effective strategies for reducing errors in adult inpatients (Bates et al. 1998; Leape et al. 1999;
Leape et al. 1993). However, much of the arguments for CPOE in children are based on extrapolation of results from adult studies (Bates et al. 1999; Bates et al. 1998; Chamberlain et al. 2004; Johnson and Davison 2004; Lehmann and Kim 2006) The most common type of medication error in pediatrics is a dosing error at the ordering stage.(Crowley et al. 2001; Leape et al. 1995; Vincer et al. 1989) The use of computerized provider order entry (CPOE) has been advocated as a response to the high rates of medication errors that have been documented in many studies. CPOE has been endorsed by the Institute of Medicine in the report To Err is Human (Institute of Medicine 1999) and by organizations such as the Leapfrog Group (Leapfrog Group 2009). The use of CPOE is one of many recommendations made by the IOM to improve patient safety by providing safer patient care and improved outcomes by decreasing the potential for medication errors.

Most of the published studies concerning the use of CPOE have come primarily from academic and government medical centers. The use of CPOE in an academic emergency department demonstrated significant reductions in prescription errors and the need for pharmacist clarification (Bizovi et al. 2002). Adverse drug events (ADEs) due to medication errors were common and many occurred at the stage of prescribing and ordering medications. In one estimate, 64.4% of errors (including 43% of potentially harmful errors) were considered preventable by the use of CPOE (with clinical decision support [CDS]) (Lehmann and Kim 2006).

Despite government and health care industry endorsements and published evidence that CPOE will improve patient safety and prevent or reduce medical errors, successful adoption is not yet widespread in the United States. By 2002, only 9.6% of a sample of United States hospitals reported complete CPOE availability, with 6.5% reporting partial availability (Ash et al. 2004). Reasons for low adoption may include issues of local feasibility. Nonalignment of user incentives and disagreements on institutional priorities may impede local adoption. Technically, the expertise needed to achieve the safety and quality benefits of CPOE while maintaining operations may exceed the capabilities and resources of the institution. Financially, the initial costs of adoption and ongoing costs of maintenance of CPOE may be prohibitive to institutions in a competitive market (Lehmann and Kim 2006). The implementation of CPOE/CDS will directly connect:

- Prescribers to data (patient records, drugs, and laboratory or radiology test results)
- Prescribers to other health professionals (nurses and pharmacists)
- Information systems to one another (patient records, drug and laboratory databases)
- Departments to one another (patient care units, physician offices, pharmacies)

On a technical level, CPOE and CDS reduce variation and provide decision support by:

- Improving legibility
- Reducing transcription errors
- Using standard names, catalogues, and dictionaries
- Linking patient-specific data and information
- Providing evidence-based order sets
- Automating calculations
- Providing alerts and reminders
- Monitoring for adherence to best practice
- Screening populations at risk

There is an assumption that a decrease in medication error rates alone is sufficient to determine the efficacy of CPOE; this endpoint does not necessarily imply improved patient outcomes and safety. In a study by King et al., the introduction of CPOE into the hospital resulted in a 40% decrease in medication error rates; however, there was no evidence to demonstrate any effect from CPOE on actual or potential patient harm (King et al. 2003). Han et al. reported an increase in the mortality rate in a pediatric ICU (from 2.8 to 6.6%) after the introduction of CPOE, likely due to delays in medication administration and less nursing time at the patient’s bedside (Han et al. 2005). In a study by Del Beccaro et al., there was no effect on mortality rates in the PICU with the introduction of CPOE (Del Beccaro et al. 2006). Clearly, there are complexities with an examination of the effects or process on patient outcomes; however, research is needed to discern the actual impact of CPOE on patient outcomes.
Summary

Chronic pain in children may be nociceptive, neuropathic, or a mixed pain etiology. The treatment of pain and suffering of children should be an important element of care. Knowledge of the developmental issues related to pharmacokinetics and pharmacodynamics will guide the clinician to a rational approach to pharmacological pain management. A thorough understanding of the mechanism of action of the pharmacologic agents will provide a safe and effective use of drugs for the treatment of chronic pain. More research is needed to determine the appropriate dosing of agents and likely efficacy for children, and the FDA is encouraging more studies in the pediatric population. The use of CPOE and clinical decision support analysis will hopefully lead to a safer system to provide analgesics to children.

References


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